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TITLE: DRAFT ON THE CLINICAL EVALUATION OF WEIGHT-CONTROL DRUGS
ACTION OFFICE HFD-7

Other ID's:

Docket Number: 2003D-0570

Document #	Received Date	Filed Date	Submitter Code	Submitter	FR Date	FR Page	Comment Date	Volume	Remarks
GDL1	01/23/2004	01/23/2004	Federal Government	Guidance Signature: Guidance				1	
N1		01/23/2004	FDA	FDA Signature: SHUREN, JEFFREY	01/26/2004	3588-3589	04/26/2004	1	
EC1	02/12/2004	02/11/2004	Individual Consumer	Atkinson, Christine Signature: Miss. Christine Atkinson				1	
C1	03/11/2004	03/08/2004	Association	American Obesity Assn (AOA) Signature: Morgan Downey				1	
EC2	03/24/2004	03/23/2004	Drug Industry	Peptimmune, Inc. Signature: Krop, Julie				1	
C2	04/16/2004	04/16/2004	Drug Industry	Abbott Laboratories Signature: Douglas L. Sporn				1	
EC3	04/16/2004	04/15/2004	Academia	Pennington Biomedical Research Center Signature: Bray, George				1	
EMC1	04/20/2004	04/20/2004	Drug Industry	Merck & Co., Inc. Signature: Donald Black, MD				1	
C3	04/22/2004	04/21/2004	Drug Industry	Eli Lilly and Company (Lilly) Signature: Gregory A. Gaich,MD and Jennifer L.				1	
C4	04/26/2004	04/23/2004	Drug Industry	GlaxoSmithKline (GSK) Signature: Maria Wagner, PhD				1	
C5	04/26/2004	04/23/2004	Drug Industry	Nastech Pharmaceutical Company, Inc. (NASTECH) Signature: Gordon Brandt, MD				1	
C6	04/26/2004	04/23/2004	Drug Industry	Hoffmann-La Roche Inc. Signature: Cynthia Dinella, PharmD				1	
C7	04/26/2004	04/23/2004	Drug Industry	Pharmaceutical Research and Manufacturers of America (PhRMA) Signature: Michael Garvin, PharmD				1	
C8	04/26/2004	04/23/2004	Drug Industry	Johnson & Johnson Pharmaceutical Research & Development, LLC Signature: Jacqueline A. Coelln, R.Ph				1	
C9	04/27/2004	04/26/2004	Drug Industry	Amylin Pharmaceuticals, Inc. (AMYLIN) Signature: Christian Weyer, MD				1	
C10	04/27/2004	04/26/2004	Drug Industry	Pfizer, Inc. Signature: William R. Murphy, PhD				1	
EMC2	04/23/2004	04/23/2004	Drug Industry	Hoffman-LaRoche, Inc. Signature: Cynthia Dinella, PharmD				1	
EMC3	04/26/2004	04/26/2004	Drug Industry	Johnson & Johnson Signature: Jacqueline A. Coelln, R.Ph				1	

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Document #	Received Date	Filed Date	Submitter Code	Submitter	FR Date	FR Page	Comment Date	Volume	Remarks
EC4	04/27/2004	04/26/2004	Drug Industry	Amylin Pharmaceuticals, Inc. Signature: Weyer, Christian				1	

003D-0570 - Guidance for Industry: GUIDANCE FOR THE CLINICAL EVALUATION OF WEIGHT- CONTROL DRUGS; Availability

FDA Comment Number : EC1

Submitter : Miss. Christine Atkinson **Date & Time:** 02/12/2004 10:02:25

Organization : Miss. Christine Atkinson

Category : Individual Consumer

Issue Areas/Comments

GENERAL

GENERAL

Weight-control drugs need to be re-evaluated. Many of these drugs are lethal or cause dehilibating diseases. The drugs that are being offered on tv and magazines that aren't approved by the FDA need new guidelines as to their labeling. In the commericials and the magazine ads they need to list the possible side effects of the drugs and that the drug is not approved by the FDA. My best friend was seriously overweight. Thankfully I was able to talk her out of using these drugs, but there are many people who take these drugs that think they are completely safe.

AMERICAN OBESITY ASSOCIATION

Advancing the Understanding of the Disease of Obesity

March 8, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane Rm. 1061
Rockville, Md. 20852

Re: FDA Guidance Document on Weight Loss Drugs
Docket No.2003D-0570

On January 31, 2003, the Food and Drug Administration (FDA) issued the paper, Improving Innovation in Medical Technology: Beyond 2002 indicating an interest in reviewing the Guidance for the Clinical Evaluation of Weight Loss Drugs (issued September 24, 1996). During this time, the Secretary of the Department of Health and Human Services, Hon. Tommy Thompson, and the Commissioner of the Food and Drug Administration, Mark McClellan, were directing public attention and internal resources to the burgeoning problem of obesity in America.

After issuance of the FDA paper, the American Obesity Association (AOA) convened a meeting of pharmaceutical companies involved in the development of drugs for the treatment of obesity. The meeting was held in April 2003 in Washington, D.C. and was addressed by Dr. Lester Crawford, then Deputy Commissioner of the FDA.

That meeting addressed issues of common interest to those engaged in the development of drugs to address the obesity epidemic. A number of specific problems with the 1996 guidances were identified. Subsequently, drafts of suggestions for changes in the 1996 guidelines were circulated for comment within the group. A second meeting of companies was held in October 2003 in Florida and to discuss revisions to the draft. A second draft of changes was circulated to which several companies responded. A writing committee was assembled to integrate suggestions into a final draft. The companies involved in this consultative process are Abbott Pharmaceuticals, Amylin Pharmaceuticals, Eli Lilly & Company, GlaxoSmithKline, Johnson & Johnson, Merck Research Laboratories, Millennium, Novartis Pharmaceuticals Inc., Pfizer Inc., Regeneron Pharmaceuticals Inc, Roche Laboratories, and Sanofi-Synthelabo Inc. (Not every company participated in every meeting.)

2003D-0570 C1

A note should be made about these topics and recommendations. The AOA-industry group tried to identify those issues about which there was general agreement on the need for change. It was recognized that each company might have concerns, which are addressed in this document and others which are not addressed. This is not to diminish the importance of the issues which are not herein addressed. Rather, this document is intended only to highlight those issues on which there is widespread agreement within the AOA-industry group. It should also be noted that, even though there was agreement in general on these issues, there was no absence of debate. There was vigorous give-and-take on many issues and a recognition that reasonable people may disagree. Our intention is to take this discussion to critical decision-makers at the Food and Drug Administration and the National Institutes of Health (NIH) for their informed consideration.

On January 26, 2004, the Food and Drug Administration issued a Request for Comments on a Draft Guidance on the Clinical Evaluation of Weight-Control Drugs. (Docket No. 2003D-0570. This cover letter and attached draft changes are submitted to the docket in the interest of the broadest public debate on this important issue.

A. The Perception of Risk-Benefit Drugs in General for the Treatment of Obesity

The history of drugs for the treatment of obesity is an unfortunate one. Early medications too often proved to be so unsafe to be removed from the market. This experience has colored the thinking of many dispensing physicians, consumers and the general public. Unfortunately, experiences with previous weight loss drugs have created a negative perception of the utility of any future drug to treat obesity.

The currently approved medications for the treatment of obesity are demonstrating safety and efficacy but there are only two such products, giving physicians and patients few options.

In general, the biomedical research and drug development community agrees with the FDA, indeed the whole of the Department of Health and Human Services, that obesity is an urgent public health issue which requires more options for medical intervention. There are millions of cases where drug intervention might be employed to reduce weight or body fat and the conditions caused by excess weight or fat. In addition, the pharmaceutical industry is excited about recent scientific discoveries, which have greatly elucidated the mechanism by which body weight is regulated. These findings have indicated several new, potential therapeutic targets that hold a promise of greater efficacy and safety than past products.

It is felt that the negative perception of drugs to treat obesity is widespread at the FDA and affects the approval process.

- Where the researchers on obesity medicines sees millions of cases of very sick persons who need to lose weight to improve their health (e.g., there are over 8 million persons with morbid obesity alone), the FDA is perceived as anticipating

that any weight loss drug will be widely used by persons who are not overweight or obese or who desire cosmetic weight loss only or will be widely abused.

- Where these researchers see many individuals unresponsive to diet and physical activity intervention, they perceive that the FDA as seeing diet and physical activity as the optimum strategy to improve all or almost all cases of excess weight.

- Where the researchers on obesity medicines see many drugs carrying as significant health risks as obesity medications, they perceive the FDA as holding weight loss drugs to a higher standard of safety.

In short, the obesity pharmacology development field sees the FDA as historically being resistant to medications to treat obesity. This is, of course, a significant concern to any company that must decide whether to allocate millions of dollars to development of a drug for obesity or some other condition. FDA's public acknowledgement of the importance of developing safe and effective drugs to address obesity and its associated morbidities is viewed as important first step in alleviating the AOA-industry group's concerns. Important progress will be made when this publicly announced change in perception is reflected in the new guidance document. An important suggestion along these lines is reflected in new language regarding Endpoints which acknowledges that changes in obesity-associated cardiovascular risk factors, both positive and negative, are valuable for determining the risk-benefit ratio of any one product. And that labeling for such important risk factors can be obtained in association with weight loss rather than independent of weight loss as presently dictated by the FDA.

B. Clinical Issues Affecting Obesity Drug Approval

The AOA-industry working group has developed a proposed draft of a guidance for weight loss drugs. Among the features of the proposed new guidance are:

1. A change in the title from drugs for weight loss to drugs for treatment of obesity and overweight.
2. The proposed draft is more descriptive of the disease process of obesity.
3. The proposed draft proposes acknowledging the public health importance of prevention of weight regain after loss and long term weight loss maintenance.
4. The proposed draft contains a new section on potential therapeutic interventions.
5. The proposed draft combines population requirements into one section.
6. The proposed draft would lower the BMI threshold from 27 with one or more comorbid conditions to a BMI of 25 with one or more comorbid conditions.
7. Language describing requirements for Phase I, II and III studies is made more congruent with guidances for other diseases.

8. The requirement that all subjects on Phase II and Phase III studies receive instruction in diet, exercise, behavior modification and other life style changes is modified to require that diet and exercise instruction is defined and standardized.
9. The requirement for a six-week run-in period where all subjects are encouraged to partake of a diet restricted and increase exercise intervention is deleted. It is felt that this requirement may skewer the results of the trial and not reflect real world conditions.
10. The proposed draft increases from two to three the possible demonstrations of efficacy. The three are:
    i. The drug effect is statistically significantly greater than placebo and the mean associated weight loss exceeds the mean placebo by 5% at the end of twelve months.
    ii. The proportion of subjects who reach a loss of 5% is significantly greater than placebo at the end of one year.
    iii. The proportion of subjects who maintain a loss of at least 5% is significantly greater in subjects on drug than those on placebo at the end of two years.

The proposed draft also acknowledges an important public health role for putative drugs which would maintain weight loss which has been achieved by other means. It was felt that this was a potentially valuable, although speculative, therapeutic area.

Finally, the AOA-industry group would prefer that the relevant end-points should reflect a medically significant loss of body fat. However, there is no consensus on what is a medically significant loss of body fat at this time. We urge the Food and Drug Administration and the National Institutes of Health to cooperate on developing the research on what is a medically significant loss of body fat and to achieve consensus on a new standard.

The AOA and industry look forward to an ongoing dialogue with the FDA and NIH as new guidances are developed.

Sincerely,

Morgan Downey
Executive Director

GUIDANCE FOR THE CLINICAL EVALUATION OF ~~WEIGHT-CONTROL~~ DRUGS FOR THE TREATMENT OF OBESITY AND OVERWEIGHT ~~(9-24-96)~~

1. INTRODUCTION

This guidance is intended to recommend clinical trials and clinical drug development programs that will provide acceptable demonstrations of the safety and efficacy of drugs to treat individuals who have ~~are~~ obesity or ~~are and~~ overweight. ~~improve health and self-esteem by reducing body fat~~. General guidelines for conduct of clinical trials (GCP) and for development of new drugs for marketing should be followed in developing such ~~weight-control~~ drugs. Only those aspects of the trials that are specific to such ~~weight-control~~ drugs will be discussed in this document. Refer particularly to the Guidelines for the Format and Content of the Clinical and Statistical Sections of New Drug Applications.

These guidelines are intended to present desirable approaches rather than mandatory standards. In part, they contain recommendations for clinical studies which are recognized as valid ~~desirable~~ approaches to be used in arriving at conclusions concerning safety and efficacy of new drugs; and in other part, they reflect the views of experts in the field as to what constitutes appropriate methods of study of specific classes of drugs. In some cases, other methods may be equally applicable or newer methods may be preferable, and for certain entirely new entities it is possible that the guidelines may be only minimally acceptable. Sponsors are encouraged to discuss approaches with staff of the Food and Drug Administration.

2. GENERAL RATIONALE

~~Excess weight is associated with excess morbidity (diabetes, hypertension, coronary heart disease, stroke and other cardiovascular diseases, hyperlipidemia, osteoarthritis, several types of cancers, gall bladder disease, sleep apnea, depression, and low self-esteem) and mortality. It seems likely that preventing obesity, and/or losing weight, might prevent or reverse at least some of these morbidities. Weight is frequently (usually) regained~~

~~the drugs have been discontinued. Certain drugs might maintain weight loss successfully in some individuals if drug administration were continued for longer periods of time. Since it is possible that a new "set point" will be developed at a reduced body mass, drug administration might be required for only a limited time; however, it is probable that drug administration must be continued indefinitely in order to reap the health and other benefits of reduced body weight. FDA standards for weight control drug approval anticipate the investigation of long-term safety and efficacy of weight control drugs, leading to approval of drugs with indications for weight control using long-term or indefinite drug administration.~~

Obesity is a long term, chronic, fatal and relapsing disease in which the principal sign is excess adipose tissue. Obesity is a phenotypic disease that has primary etiologies (e.g. "primary obesity", hypogonadoptropic hypogonadism, Prader-Willi syndrome), secondary etiologies (e.g. Cushing's disease, hypothyroidism) and may even be drug induced. The etiology of "primary obesity" is multifactorial. Increased adiposity is caused by genetic, environmental, behavioral and hormonal factors. It has been established that there are neuroendocrine factors that affect body mass, appetite, and satiety.

Excess adiposity alone causes a number of changes in the body's lipids metabolism. Obesity significantly affects the musculoskeletal and cardiovascular systems.

Obesity is well established as a cause of many important health conditions (referred to as comorbid conditions) including type 2 diabetes, heart disease, hypertension, stroke, dyslipidemia, metabolic syndrome, sleep apena, osteoarthritis of the knee and hip and some cancers. Obesity is strongly associated with numerous, other adverse health conditions, including but not limited to depression, reproductive disorders including birth defects, reduced quality of life and psychosocial problem. Obesity is known to be the second leading cause of preventable deaths in the United States and may exceed tobacco smoking as the leading cause in the near future.

Obesity has reached epidemic proportions in the United States not only among adults but among children and the elderly as well. Over 30% of adult Americans and 15% of children and adolescents are obese. The rates of obesity are also increasing among the nation's children and adolescents. This trend is especially troubling are the adverse

nation's children and adolescents. This trend is especially troubling are the adverse consequences of obesity, such as type 2 diabetes are ocurring in younger population and will persist for longer period of time. The United States has experienced consistent increases in the rates of obesity for the last thirty years. There are no signs of significant change in the trend to higher rates of obesity. The rate of obesity is much higher in some ethnic groups. The adult population with morbid or severe obesity (approximately 100 pounds overweight or a Body Mass Index > 40 kg m^2) is nearly 9 million persons. It is recognized as a major public health problem, which will shorten the duration and degrade the quality of life of millions of Americans.

Obesity may be measured in several acceptable ways. The most definitive measure is body fat mass. Surrogate measures are excess pounds over a healthy weight, waist circumference, the Body Mass Index (BMI), excess weight or waist to hip ratio. The National Institutes of Health, the Centers for Disease Control and Prevention and the World Health Organization have used the BMI scale. Based on relative mortality risk rate in adults, underweight is defined as a BMI <18.5 kg/m^2, normal is defined as a BMI 18.5-24.9 kg/m^2, overweight is defined as a BMI 25.0-29.9 kg/m^2, and obese is defined as a BMI >30.0 kg/m^2. BMI does not distinguish size that is due to bone and muscle from that due to fat, nor does it identify subjects with visceral obesity, a potent predictor of morbidity. Selected populations, such as Asian-Americans, children and adolescents may have different definitions of health risks due to obesity.

3. Potential Therapeutic Indications

Obesity is a complex, multifactorial disease that may differ among individuals based on race, ethnicity, genetic difference, or other underlying disorders, and may differ in a a given individual across time. Therefore, multiple potential therapies may be indicated. Loss of body fat or body weight as a surrogate of fat loss is one goal. Depending on the circumstances, fat or weight loss over the short term, intermediate tem, or long term may be appropriate goals for a weight loss drug. Prevention of weigh gain in hight risk individuals due to genetic or acquired factors may be an appropriate goal. Finally, maintenance of weight loss or prevention of weight gain in individuals who have lost weight may be an appropriate goal.

To achieve one or more of the above goals, single drugs or drugs in combination may act act on one or more mechanisms that promote excess adiposity. These may include reduction of hunger appetite, enhancement of satiety, alteration in food preferences, enhancement of physical activity, increases in energy expenditure or enhancement of fat oxidation. In addition to the known mechanisms of increased adiposity listed above, a drug may be targeted at novel mechanisms or strategies that are at this time are unknown.

4. Population

For most ~~weight-control~~ obesity and overweight drug studies, subjects in ~~long-term~~ clinical trials should ~~be moderately to markedly obese with~~ have a body mass index (BMI) of at least 30 kg/m^2 or greater for otherwise healthy individuals, or a BMI at least 25 kg/m^2 or greater in individuals for with one or more comorbid conditions (such as,those described in Section 2). It is of interest to identify obesity by methods that measure percent body fat and fat distribution. Drug developers may use any scientifically acceptable measurement definition. ~~Type of obesity (peripheral or central, as indicated by measures of central obesity, such as waist-hip ratio or sagital diameter), presence and severity of risk factors and related co-morbidities, severity of obesity, and duration or age at onset of obesity may be factors that should be selected, excluded or stratified. Ideally, the population will include minorities and both sexes in numbers adequate to allow measurement of response separately in men and women, and in blacks, caucasians, and hispanics.~~ Methods used to recruit subjects for obesity drug trials should be noted. Demographic data appropriate to the target population should be obtained. If relevant to the desired indication, population might include children, adolescents, the adult population, both genders, the elderly or racial, gender, and ethnic groups. Therapy for specific etiologies of obesity (e.g. hypogonadotropic hypogonadism, Prader Willi syndrome) may be considered for certain medicines.

~~subjects~~subjects who are ~~otherwise -~~ free of other diseases. ~~It is desirable to include minorities (blacks and Hhispanics in particular) and both males and females in the clinical studies~~These clinical studies include~~ing~~ the earliest studies of safety, ~~tolerance~~ tolerability, pharmacokinetics (if applicable), pharmacodynamics, ~~mechanism of action~~, and dose determination. ~~The mechanism of action of the drug should be established if possible~~.

6.~~DOSE RANGE FINDING~~ PHASE II STUDIES

~~Because a drug for weight loss may be prescribed extensively for relatively healthy subjects, it is particularly important that the drug dose recommended not be excessive. Dose-finding should identify the lowest dose of the drug that safely achieves an optimal drug effect. Inclusion of at least 3 doses of drug in dose-finding efficacy studies will probably allow identification of a low dose that is inadequate, and also a dose that achieves the maximum benefit that cam be obtained without toxicity~~. Phase II trials should be designed to obtain guidance for the design of Phase III trials and to validate proof of concept in a small number of affected individuals. The goals of Phase II studies are to capture information on safety, efficacy and dose response in the target population. They should obtain working estimates of the nature and severity of the most common side effects commonly associated with the new product. Patient history may include a number of factors, such as family history, alcoholic intake, tobacco use, exercise/activity level and dietary habits. Dietary and activity regimens should be defined and standardized within a trial and as appropriate for the patient ~~Trials~~population. Trials should usually be randomized, double-blind, and placebo controlled~~, with all subjects, both on drug and placebo, receiving similar instruction in diet, exercise, behavior modification and other life-style changes, such as use of tobacco and alcohol. This does not mean that all studies must be conducted in patients that are practicing these life-style changes, but that in all studies instructions on life style should be similar in drug and placebo groups. Generally, subjects should be moderately to markedly obese (BMI at least 30 is suggested; other obesity measures may be preferred) but subjects may be healthy otherwise. The population should include minorities and both sexes if the target~~

~~population is, broadly, overweight Americans. It is likely that 3-6 month studies in about 200 subjects will be required to show preliminary efficacy of the drug, but actual number depends on the amount of difference observed between the efficacy of drug and of placebo.~~

7.~~TRIALS TO ESTABLISH EFFICACY~~ PHASE III TRIALS

Trials to establish the safety and efficacy of a ~~weight loss~~ drug for the treatment of persons with obesity and overweight should be randomized, double-blind, and placebo-controlled.Dietary and activity regimens should be defined and standardized within the trial as much as possible in the population. ~~with all subjects, whether on drug or placebo, receiving similar instruction in diet, exercise, behavior modification and other life-style changes. For the long-term efficacy studies, it is preferable to instruct all subjects in the relevant life-style modifications~~. . Patient history may include a number of factors, such as family history, alcoholic intake, tobacco use, exercise/activity level and dietary habits. Dietary and activity regimens should be defined and standardized within a trial and as appropriate for the patient.

~~5.1 Population~~

~~For most weight-control drug studies, subjects in long-term trials should be moderately to markedly obese with body mass index (BMI) at least 30 for otherwise healthy individuals, and BMI at least 27 for those with comorbid conditions (hypertension, hyperlipidemia, glucose intolerance, cardiovascular disease, sleep apnea, or other obesity-related conditions). However, BMI does not distinguish size that is due to bone and muscle from that due to fat, nor does it identify subjects with visceral obesity, a potent predictor of morbidity. It is often preferable to identify obesity by methods that measure body fat and its distribution.~~

~~Type of obesity (peripheral or central, as indicated by measures of central obesity, such as waist-hip ratio or sagittal diameter), presence and severity of risk factors and related co-morbidities, severity of obesity, and duration or age at onset of obesity may be factors~~

~~that should be selected, excluded or stratified. Ideally, the population will include minorities and both sexes in numbers adequate to allow measurement of response separately in men and women, and in blacks, caucasians, and hispanics. Methods used to recruit subjects for obesity drug trials should be noted. Race, socioeconomic status, and education should also be included in demographic data.~~

~~5.2 Procedures~~

~~A. Subject Selection.~~

~~Subjects who meet the entry criteria with regard to obesity and risk factors may be entered into a program aimed at weight reduction, but without drug. Such a program might include calorie-restricted or controlled diet, behavior modification, and exercise. As a minimum, a modestly restricted diet and regular exercise should be actively encouraged.~~

~~Placebo may be used during this period so that placebo responders are identified. Generally, this program should be continued for 6 weeks. Subjects should not be placed on drug as long as weight loss continues without drug, but may be randomized when weight has plateaued, as long as their weight remains above their goal for weight reduction (e.g. ideal body weight). Although subjects who are still losing or who reach ideal body weight on this program have no need for drug at that time, they may be kept on the weight program and randomized to placebo or study drug later if their success at weight loss evaporates. It is possible that the principal benefit of drug over placebo will be in maintaining weight loss. In this case, the studies that are of sufficient duration to detect a difference between drug and placebo in long-term maintenance of a loss obtained with the drug of interest or with other modalities (very low calorie or formula diet, intensive diet and exercise, etc.) will be most useful for demonstrating efficacy and for dose determination.~~

7.1 ~~B.~~ Endpoint evaluation

Actual weight loss should be reported_, ~~and, also~~, It is helpful to express weight loss in relative terms such as per-cent of initial body weight~~t or percent of excess over ideal body weight~~ or change in body mass index. It is preferred that the product show a loss of body fat compared to placebo in at least one trial but weight is an appropriate surrogate for body fat. Measurement of change in central obesity is also useful.

At least ~~two~~ three ~~weight loss~~ demonstrations of efficacy are possible:

1.demonstration that the drug effect is statistically significantly greater than the placebo effect and the mean drug-associated weight loss exceeds the mean placebo weight loss by ~~at least~~ 5% for the last month at the end of one year compared to original body weight or a comparable amount of body fat.

2.demonstration that the proportion of subjects who reach ~~and maintain a loss of at least~~ a a loss of 5% of their initial body weight is statistically significantly greater in subjects on drug than in those on placebo at the end of one year.

3. demonstration that the proportion of subjects who maintain a loss of at least 5% of their initial body weight is significantly greater in subjects on drug than in those on placebo at the end of two years.

Changes in risk factors or in waist to hip circumference or sagital diameter may be appropriate endpoints depending on the population to be studied. Delay in the onset ~~Development~~ of diabetes, dyslipidemia, hypertension, cardiovascular events,osteoarthritis or other complications of obesity (See Section 2) ~~may be a suitable endpoint in certain cases~~ are desirable endpoints but not required for registration.

Measurement of obesity-associated cardiovascular risk factors (e.g. lipids, blood pressure and glucose tolerance, type 2 diabetes) during drug administration may be~~is~~ encouraged, as they may have a place in determining the balance of benefit vs risk for the drug. If one or more of these factors deteriorates or is not improved, the risk associated with this deviation must be considered in making a benefit-to-risk decision for the drug. Likewise, a drug may demonstrate both weight loss and reduction in obesity-associated cardiovascular risk factors mentioned above. Improvements in such factors must be

considered in making a benefit-to-risk decision for the drug and should be described in the label as a benefit of the drug.

It may be advantageous to determine effects of drug induced weigh loss on quality of life and related factors. Favorable changes in risk factors and quality of life may be mentioned in the package insert and might lead to an indication for risk factor alteration. The effect need not be independent of weight or fat loss. Treatment of hypertension, lipids or type 2 diabetes may be a suitable indication.

~~It may be advantageous to determine effects of drug-induced weight loss on quality of life and related factors. Favorable changes in risk factors and quality of life may be mentioned in the package insert and might lead to an indication for risk factor alteration. Treatment of hypertension or type 2 diabetes may be a suitable indication.~~

Weight loss achieved with calorie restriction alone is usually associated with loss of both fat and muscle tissue. Exercise has been reported to reduce or eliminate muscle loss. A carbohydrate-restricted regimen will usually result in loss of body water. For these reasons, it may be desirable in a suitable number of patients and in at least one trial, at the start of the trials, to establish that the subjects have excess body fat by one or more of the accepted measurements, such as skin fold thickness, body circumferences or sagital diameter, under-water weighing, bioelectric impedance, ~~and~~ DEXA, CT scan or MRI. Follow-up measurements can then confirm that body fat is decreased commensurate with the weight loss and that weight loss is not associated with excessive loss of body water or muscle. ~~It may be of some interest to detect any change in visceral obesity, or in the small dense LDL that might be present in patients with abdominal obesity.~~

7.2 Duration of Trials

The duration of clinical trials must be consistent with the selected endpoint. Drugs must be viewed as part of a long-term strategy for weight management. Drugs may be indicated for long-term weight loss and weight maintenance or weight gain prevention. The demonstration of efficacy for long-term drug use, will usually include demonstration

that the difference in weigh loss between placebo and active drug ~~effect on weight~~ is maintained for at least 12 months~~, i.e., the above mentioned (See5.2 Endpoint Evaluation) conditions for demonstrating efficacy continue to 12 months after the initiation of treatment~~. Weight loss maintenance might decrease over time in both drug and placebo groups, even resulting in reversal of efficacy. Unless significant weight loss is maintained for at least 12 months, benefits on health and quality of life may be lost. In order to obtain an adequate estimation of the safety of weight-control drugs for long-term weight maintenance ~~administration~~, subjects may be rerandomized to active versus placebo and followed for an additional 12 months (total of 2 years) ~~generally, about 1500 subjects are expected to complete 12 months with 200-500 of those subjects completing 24 months of study~~. ~~Most often the double blind status of the study is maintained for at least 1 year, at which time, placebo patients may be switched to drug and followed on open label for another 12 months to a total of 24 months for weight and development of obesity-related morbidities. For those who have dropped out of the study it is usually possible to obtain at least telephone contact at 24 months for self-reported weight, and morbidities.~~

It is not intended that this Guidance apply to all possible ~~weight-loss~~ drug evaluations for overweight and obesity. Special circumstances will obtain if the populations or endpoints are not those envisioned in the Guidance. For example, it may be desirable to study a non-obese population for prevention of weight-gain, such as during cigarette withdrawal. Such specific indications may be proposed, with the appropriate rationale, to the Division of Metabolic and Endocrine Drug Products in order to obtain input on the proposed drug program.

As new drug entities with new modes of action are developed, modifications of the Guidance may become necessary and will be considered

This document is an informal communication under 21 CFR 10.90(b)(9) that represents the best judgment of the Division of Metabolic and Endocrine Drug Products at this time. This document does not necessarily represent the formal position of the Center for Drug

303 Evaluation and Research or the Food and Drug Administration, and does not bind or
304 otherwise obligate the Center or Agency to the views expressed.
305
306 The FDA published Good Guidance Practices in February 1997. This guidance was
307 developed and issued prior to that date.
308
309 Division of Metabolic and Endocrine Drug Products, Food and Drug Administration,
310 5600 Fishers Lane, HFD-510, Rockville, Maryland 20857-1706 (301) 827-6430

2003D-0570 - Guidance for Industry: GUIDANCE FOR THE CLINICAL EVALUATION OF WEIGHT- CONTROL DRUGS; Availability

FDA Comment Number : EC2

Submitter : Dr. Julie Krop **Date & Time:** 03/30/2004 05:03:07

Organization : Peptimmune, Inc.

Category : Drug Industry

Issue Areas/Comments

GENERAL

GENERAL

1. Expectation of a 6 week run in period with plateau of weight prior to randomization is very unrealistic as a requirement for phase 2/3 weight loss studies-
2. Given current obesity epidemic and need for new therapys, agents with limited toxicity concerns should be able to file for approval with 1 year data and allowed to submit 2 year data during approval process.

ABBOTT LABORATORIES
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April 15, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2003D-0570, CDER 2003186. Request for Comments on the Draft Guidance on the Clinical Evaluation of Weight-Control Drugs.

Abbott Laboratories (Abbott) is very pleased to have the opportunity to comment on the Draft Guidance on the Clinical Evaluation of Weight-Control Drugs, published in the Federal Register on January 26, 2004.

While supporting, in general, the Pharmaceutical Research and Manufacturers of America's (PhRMA) position on this draft guidance, Abbott would like to thank the Agency for their consideration of the following attached comments.

Should you have any questions, please contact Ivone Takenaka, Ph.D. at (847)-935-9011 or by FAX at (847) 938-3346.

Sincerely,

Douglas L. Sporn

2003D-0570 C2

Abbott

April 15, 2004

Comments on the Draft Guidance for the Clinical Evaluation of Weight-Control Drugs

Docket No. 2003D-0570

The following comments are provided on behalf of Abbott Laboratories (Abbott).

Sections 1 and 2. INTRODUCTION and GENERAL RATIONALE

Abbott recommends the Introduction and General Rationale sections be revised by considering the following observations.

Obesity is a worldwide public health problem, afflicting more than 300 million people.[1] In the United States, approximately 300,000 deaths per year may be attributed to obesity.[2] The World Health Organization (WHO) considers obesity a global epidemic.[3] There has been a dramatic increase in the prevalence of obesity over the past decades.[4] The 1999-2000 National Institutes of Health Examination Survey (NHANES) indicates 64.5% of US adults are overweight and 30.5% obese.[5] Of concern 15.5% of adolescents aged 12-19 now exceed the 95th percentile for age-and sex-specific measures of Body Mass Index (BMI).[6] A recent Surgeon General's report identified obesity as a national priority for treatment.[7] The Secretary for Health and Human Services Tommy Thompson calls overweight and obesity "among the most pressing new health challenges we face today" [8] and the Commissioner of Food and Drugs, Mark McClellan has acknowledged that "we have an obesity epidemic in this country, with about two-third[s] of Americans overweight, and a third obese and [at] heightened risk for many health problems."[9]

In adults, overweight and obesity are defined as a BMI of 25.0 to 29.9 kg/m^2 and ≥ 30 kg/m^2, respectively.[10] Studies show that mortality begins to increase with a BMI > 25 kg/m^2.[11] The increase in mortality rates is primarily associated with obesity-related cardiac and vascular complications. Significantly increased risk of death from cardiovascular disease was noted in women with a BMI greater than 25.0 and in men with a BMI greater than 26.5.[12] According to the Nurses' Health Study involving 115,195 women followed over a period of 16 years, the risk of death was 60-70 percent higher among subjects with a BMI between 29 and 32 compared to subjects with a BMI between 25 and 27.[13] The risk of morbidity related to a number of health conditions such as hypertension, dyslipidemia, and glucose control rises with increasing BMI.[14] In addition, obesity is a well-recognized risk factor for type 2 diabetes mellitus,[15] gallbladder disease,[16] osteoarthritis,[17] sleep apnea and other respiratory problems,[18] and certain types of cancers (*e.g.*, endometrial, breast, prostate, and colon).[19]

The effect of obesity on cardiovascular morbidity and mortality has been associated with hypertension, diabetes and hyperlipidemia. Increased blood pressure is a well-known cardiovascular risk factor. About two-thirds of all patients with hypertension are either

overweight or obese.[20] In the Framingham study,[21] for every 10% rise in relative weight, systolic blood pressure rose by 6.5 mmHg, fasting cholesterol by 12 mg/dL (0.3 mmol/L) and fasting blood glucose by 2 mg/dl (0.11 mmol/L). Increased blood pressure has been linked to increased risk for stroke, coronary heart disease, and all-cause mortality after a mean of 10 years of follow-up (range 6-25 years).[22]

One of the benefits expected from weight loss is the reduction in blood pressure that may offset pre-existent hypertension or improve blood pressure control. Moderate weight loss using a variety of dietary approaches has been correlated to blood pressure reduction of approximately 1 mm Hg systolic (SBP) and 2 mm Hg diastolic (DBP) for each 1% reduction in body weight.[23] Pooled results from dietary intervention trials showed that a mean weight difference of 9.2 kg compared to the control group was associated with 3 mmHg lower DBP and 6 mm Hg lower SBP.[24] Data accrued during the past 20 years from population studies[25] confirm that both SBP and DBP have continuous and graded relationships to cardiovascular outcomes in men and women, independent of other known risk factors.

The location of body fat is also a predictor of the relative health hazards of obesity. Epidemiological studies have shown that the regional distribution of body fat is a significant and independent risk factor for cardiovascular disease. Accumulation of adipose tissue in the abdominal region (visceral adiposity), which is estimated by the waist circumference, correlates with increased risk of cardiovascular disease and premature death. [26], [27], [28], [29] Subjects with visceral obesity represent a subgroup of obese individuals with the highest risk for cardiovascular disease and who are also at greatest risk for metabolic complications compared to patients with lower body obesity. Visceral adiposity, in particular, is related to dyslipidemia, insulin resistance (detected by measuring high insulin levels) and is predictive of an increased risk for type 2 diabetes mellitus.

The prevalence of type 2 diabetes mellitus has tripled in the past 30 years in parallel with the upsurge in obesity. A subanalysis of the Nurses' Health Study found that a weight gain of 7- to 10-kg after 18-years of age was associated with a twofold increase in risk of diabetes and an adult BMI of ≥31 was associated with a 40-fold increased risk.[30] The Finnish Diabetes Program[31] and the Diabetes Prevention Program[32] showed that overweight patients who lost approximately 5% of their body weight reduced their risk for developing type 2 diabetes by 58%. Intentional weight reduction of any amount in women 40- to 60-years of age that had never smoked reduced all-cause mortality by 20% and diabetes-associated mortality by 30 to 40%.[33] Clinically significant improvements in lipid abnormalities,[34] glycemic control[35] and hypertension,[36] have also been associated with modest weight reduction.

Epidemiological evidence suggests that low HDL levels and increased triglyceride levels are independent risk factors for cardiovascular disease.[37], [38], [39] Results from two landmark trials, VA-HIT[40] and the Helsinki Heart Study,[41] showed that raising HDL

and lowering TG levels (with gemfibrozil, in men only), even without lowering LDL levels, reduced death from coronary heart disease and nonfatal myocardial infarction and stroke, in subjects whose primary lipid abnormality was low HDL. Specifically, a 6-8% increase in HDL levels was associated with a 23-24% reduction in the composite of these events.

Taken together, overweight and obesity should be considered as serious medical conditions that require therapeutic options to be made available to patients as part of a comprehensive weight loss program that may include drug therapy. The known long-term risks of overweight and obesity necessitate action by the FDA to provide an appropriate medical perspective for this condition. It has been well established in the literature that modest weight loss, in the range of 5-10% of initial body weight, is sufficient to improve obesity-related conditions.[42]

3. **EARLY CLINICAL TRIALS (suggestion: rename as Phase I)**

4. **DOSE RANGE FINDING (suggestion: rename as Phase II)**

- The first sentence of this section "*Because a drug for weight loss may be prescribed extensively for relatively healthy subjects, it is particularly important that the drug dose recommended not be excessive*" does not seem relevant. Dose-ranging studies for compounds are designed to identify an effective dose for Phase III trials ultimately to provide an appropriate dose in support of an acceptable benefit/risk assessment. It does not seem relevant to point this fact out specifically for treatment of overweight and obesity.

- Inclusion criteria should be revised to reflect the WHO and the National Heart, Lung and Blood Institute (NHLBI) recommendations: Overweight and obesity in adults are defined as a BMI of 25.0 to 29.9 kg/m^2 and ≥ 30 kg/m^2, respectively.[43] The rationale behind these definitions is based on epidemiological data that show increases in mortality with BMIs above 25 kg/m^2. The increase in mortality tends to be modest until a BMI of 30 kg/m^2 is reached. For persons with a BMI of ≥ 30 kg/m^2, mortality rates from all causes, and especially from cardiovascular disease, are generally increased by 50 to 100 percent above that of persons with BMIs in the range of 20 to 25 kg/m^2. In epidemiological studies, BMI is the favored measure of excess weight to estimate relative risk of disease. Moreover, calculating BMI is simple, rapid, and inexpensive, and can be applied easily to adults.[44]

- Abbott recommends that requirements relevant to number of patients and duration of study be removed. These requirements may vary depending on the nature of the compound in development and the mechanism of action. Therefore, the specific requirements for these factors should be defined

through discussions between the sponsor and FDA during the development of the drug.

5. TRIALS TO ESTABLISH EFFICACY (suggested: rename as Phase III)

5.1. Population

- Inclusion criteria should be revised to reflect the WHO and NHLBI recommendations: Overweight and obesity in adults are defined as a BMI of 25.0 to 29.9 kg/m^2 and ≥ 30 kg/m^2, respectively. [45]

- The final paragraph of this section, "*Methods used to recruit subjects for obesity trials should be noted. Race, socioeconomic status, and education should also be included in demographic data*" should be modified. Abbott recommends that socioeconomic status and education be removed and only race be included as part of the demographic information. Only racial differences have been noted in the prevalence of obesity and related complications.

5.2. Procedures

- Candidates for weight management trials should be subjects who have not been successful with diet and exercise, as noted in the NHBLI guidance. The NHBLI guidance recommends that all subjects meeting the BMI criteria, as defined in the treatment algorithm, should attempt to lose weight.[46] The three major components of weight loss therapy are dietary therapy, increase physical activity and behavior therapy. Lifestyle therapy should be tried for at least 6 months before considering pharmacotherapy.[47] A short run-in phase may be considered to familiarize the patients with the behavioral modification program.

- Abbott concurs that the principle benefit of a drug over placebo might be either weight loss or weight maintenance.

Endpoint Evaluation

- Regarding criteria one and two for weight-loss demonstrations, Abbott agrees with these criteria as a 5 % reduction in weight has been associated with improvement of obesity-related conditions in adults.[48] The Finnish Diabetes Program[49] and the Diabetes Prevention Program[50] showed that overweight patients who lost approximately 5% of their body weight reduced their risk for developing type 2 diabetes by 58%.

- Abbott contends that treatment duration for the clinical trial should not be defined in this section as was recommended by the American Obesity Association in their letter to the Division of Dockets Management dated March 8, 2004. The issue of duration of trials is discussed in another section of the Guidance document. Any description of duration of trial should be stated in a general nature such as "at the endpoint".

- Regarding paragraphs "*Changes in risk factors or in waist to hip circumference or sagital diameter may be appropriate endpoints depending on the population studied. Development of diabetes or other complication of obesity may be a suitable endpoint in certain cases,* "and "*It may be advantageous to determine effects of drug-induced weight loss on quality of life and related factors. Favorable changes in risk factors and quality of life may be mentioned in the package insert and might lead to an indication for risk-factor alteration. Treatment of hypertension or type 2 diabetes may be a suitable indication.*" As previously provided, weight reduction impacts obesity related conditions, quality of life and/or risk factors and, as such, should be considered as potential outcomes or indications for treatment.

  Incorporating "delay to onset" along with 'development of" for risk-factors would be an appropriate addition to the above as an option of study design. The weight-loss endpoint, however, as described in the guidance document should continue to be the focus for registration as defined by the weight-loss criteria set forth in the draft guidance document. Other options provided by the above would be considered optional to the sponsor.

- Last sentence of section 5.2, "*...or in the small dense LDL that might be present in patients with abdominal obesity*" should be amended to reflect the fact that LDL cholesterol is not directly related to visceral adiposity.

5.3 Duration of Trials

- Abbott recommends that the exposure requirement defined by the draft Guidance be removed, as these requirements will largely depend on the compound being developed and experiences with marketed drugs in a similar class.

- The duration of the efficacy study may depend on the intended use of the drug, i.e., short-term weight loss and / or long-term weight maintenance.

- This criterion should be defined through discussions between FDA and the sponsor during development, e.g., pre-IND meeting.

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2003D-0570 - Guidance for Industry: GUIDANCE FOR THE CLINICAL EVALUATION OF WEIGHT- CONTROL DRUGS; Availability

FDA Comment Number : EC3

Submitter : Dr. George Bray **Date & Time:** 04/19/2004 03:04:23

Organization : Pennington Biomedical Research Center

Academia

Category :
Issue Areas/Comments

GENERAL

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We view the procedures for evaluating a drug in the treatment of obesity as an opportunity to demonstrate the efficacy of the drug and its high level of safety; considering the population in which it will be used, we also view this process as a basis for developing information about the use of a drug by physicians in the practice of medicine and the care of their patients.

Re: Docket Number 2003D-0570:
Comments on Clinical Evaluation of Weight Control Drugs Guidance issued 9-24-96

Thank you for the opportunity to provide my ideas about the procedures for the Clinical Evaluation of Weight Control Drugs as outlined in your Guidance document of 9-24-96. Prior to the issuance of this Guidance, Dr. Leo Lutwak had convened an expert panel to give input to the FDA about this problem. One signatory to this letter (GAB) was one of those initial participants. More than a decade has passed since this conference, and we are pleased to provide you with our current ideas.

General Comment: We view the procedures for evaluating a drug in the treatment of obesity as an opportunity to demonstrate the efficacy of the drug and its high level of safety; considering the population in which it will be used, we also view this process as a basis for developing information about the use of a drug by physicians in the practice of medicine and the care of their patients.

Paragraph by Paragraph Comments:

1. Introduction: Well done.
2. General Rationale:

a. In the middle of this paragraph it says: "Since it is possible that a new "set point" will be developed at a reduced body mass, drug administration might be required for only a limited time"; for the purpose of drafting a new Guidance, this statement should be removed. We know of no evidence that obesity can be cured. Years ago, the rationale for the jejuno-colic by-pass was that when patients lost weight the operation would be reversed they would be able to maintain the lower weight. As Payne et al [1] found, to their chagrin, all of the patients regained weight after reversal. Since, in our view, obesity is a "chronic relapsing neurochemical disease" [2], it is only a matter of time after any treatment is discontinued before weight will return to "baseline". However, this doesn't mean that treatment needs to be "continuous". At least two studies using discontinuous therapy with anti-obesity drugs [3]; [4] demonstrate that anti-obesity drugs produce as much weight loss at 9 or 12 months as continuous therapy. Indeed, trials with intermittent therapy might be worth evaluating.

b. Weight loss has two components. One is medical and one is cosmetic. When health is at risk, the potential risks of a drug can be greater than when the goal is cosmetic. Since the majority of patients seek weight control for "cosmetic" reasons, safety concerns become more important than if people were only using them were for high risk of diabetes, gall bladder, cardiovascular or other diseases. Since the motivations for taking these medications will be the desire to "look good," and the desire to improve the quality of life is an important

medical end-point, recognition that anti-obesity drugs will have BOTH cosmetic and medical uses is important in designing trials and in developing information for the physician and consumer.

c. Length of clinical trials. Although anti-obesity drugs may have long-term use, for most consumers the continuous use is likely to be only a few weeks to a few months. This is true for two reasons. First, clinical trials for weight loss demonstrate that weight loss ceases after 4 to 8 months of treatment – a plateau develops. This occurs with behavioral, dietary, medical and surgical interventions. It is the nature of a homeostatic, compensatory system. However, when weight loss does reach a plateau that plateau is often less than 10% of initial body weight and many patients discontinue the medication because they conclude that the medication "isn't working". Moreover, discontinuation is more likely if the medication is expensive. We know from experience with over-the-counter herbal ephedra preparations that consumers will pay up to $30/month for fairly long term use. However, we also know from the experience with sibutramine and orlistat that they will not pay $100/month for an equivalent amount of weight loss. Thus the interaction of cost and the compensatory plateau make it unlikely that many consumers will use anti-obesity drugs for an extended time – at least not with any current drug. However, they will typically use them for short periods when weight loss is needed for cosmetic reasons such as a wedding, a divorce, a reunion or to achieve a personal weight goal.

3. Early Clinical Trials. The statement is very clear and useful.

4. Dose-ranging Finding. The criteria for designing the initial dose-ranging studies are clearly stated. Because only 75% of the maximal weight loss is achieved by 3 months, trials of 6 months might be more appropriate. We would also prefer the trial to begin without a "run-in" period, unless the run-in is to establish tolerability to the medication procedure without other active (lifestyle or diet) therapy.

5. We will take this section paragraph by paragraph.

5.1 Population: The current Guidance was written before the NHLBI and WHO provided uniform recommendations for classification of obesity. We would encourage the FDA to include in their trials individuals with a BMI > 25 kg/m^2 since all of our epidemiological data, particularly that for diabetes, shows that the risks of disease begin at that level. The selection of 27 kg/m^2 with co-morbidities harks back to the days when the NCHS was using the 27.3 and 27.8 kg/m^2 BMI unit cut-points to define overweight. Now that these cut-points are no longer used, the FDA might want to seriously reconsider its selection of 27 kg/m^2 and move to 25 kg/m^2. Measuring body fat can be useful, but the BMI and waist circumference have proven to be very useful criteria for assessing risk [5]; [6]; [7]. Measurement of waist/hip ratio and sagittal diameter have nothing over the simple measurement of waist circumference, and I would recommend that the waist circumference be used along with the BMI.

5.2 Procedures:

Subject Selection: We strongly object to the use of the run-in for clinical trials of anti-obesity drugs. It is confusing to the physician, to the patient, and not instructive for the effect of the drug. When a patient receives medication from a physician for the treatment of obesity, what both the doctor and patient want to know is how much weight loss their patient is likely to achieve, and what side effects might occur. The idea of "placebo-subtracted" weight loss is unhelpful to either physician or patient. Similarly, few physicians have the office set-up to conduct an active lifestyle change program or to give diet counseling. An effective anti-obesity medication will usually be used with minimal behavioral or lifestyle therapy. Thus, for both patient and physician, knowing how much weight loss is achieved from initiation of the drug is the question of interest, NOT how much weight loss might occur after an active lifestyle or dietary intervention. Thus, we think the run-in should be eliminated or shortened to a non-therapeutic period of 1 week.

We like the discussion of the weight maintenance strategies at the end of paragraph 5.2. These have proven to be very useful and important.

End-point evaluation. Since men and women are included and they have different percentages of body fat and often different initial body weights, we would prefer to have the primary end-point the Percent Change in Body Weight. Since height doesn't change, the change in BMI provides no more information than the change in body weight, and is a more cumbersome unit for weight loss. We would NOT just use change in BMI. Change in body fat in kg and % separated by genders would also be useful, as would changes in visceral adipose tissue in a subsample.

Weight loss demonstrations. We would prefer a criterion of >5% from baseline and significantly greater than placebo. At present, no drug consistently meets the criterion of 5% below placebo. To require a drug to be >5% below placebo encourages trials with a "weak" placebo effect to make it easier to see the 5% criterion. This in turn penalizes long-term trials, since patients on placebo losing only small amounts of weight are likely to drop out. Although we would like drugs to produce >10% below baseline as monotherapy, almost none have done so, and if this were the criterion, we might have no drugs at all. Moreover, for many people a weight loss of 5-10% is sufficient for the "cosmetic" effects that are often wanted. It will also produce significant health benefits [8]; [9].

The use of improvements in "risk" factors is good. We would drop sagittal diameter and use waist circumference. Studies in diabetic populations and hypertensive populations are valuable.

Since in many patients with recent onset diabetes, weight loss can lead to remission, it might be claimed that drugs producing weight loss are "anti-diabetic" drugs. We would not favor this position. If the drug doesn't have an independent

effect of glucose metabolism or the action of insulin, we would not favor approving it for diabetes. Weight loss in diabetics and pre-diabetics, on the other hand, is clearly beneficial, because it will lower the cost of treatment for diabetes and may lead to remission. Thus, weight loss drugs might be labeled as weight loss adjuncts for the treatment of diabetes.

Improvement in the quality of life is one of the major reasons that most people seek help with their weight. Having some measure of how much improvement there is would be valuable.

Except in the very obese, the issue of excess fluid does not exist. When we measured intracellular and extracellular water in a group of obese patients, the only ones with abnormal distributions were those who were "very" obese, i.e., more than 400 pounds. However, we think documentation of the extent of change in lean body mass and calcium loss (DXA bone changes) could be considered in a subset of patients.

5.3 Duration of Trials. We would propose that a 12-month double-blind, randomized, placebo-controlled trial should demonstrate 5% or greater reduction from baseline weight for the drug-treated group at 12 months that is also significantly lower than placebo. Viewing the 4-year XENDOS trial [10] the drug-treated group and placebo-treated group both began to regain weight following the plateau at 12 months, but the drug-treated group remained more than 2% below the placebo-treated group even after 4 years. Unless there is evidence of escape from the therapeutic effect of the drug as occurred with fluoxetine [11], we think that a 12-month trial is sufficient to show efficacy and safety.

The issue of follow-up and handling of drop-outs is an important one. Our experience with follow-up after discontinuation from a clinical trial is dismal. If patients quit they usually don't want to be followed up by phone or otherwise. With our current IRB constraints the problem is even more difficult. For the package insert, we would propose that only the completers analysis be used. What the physician and patient both want to know is how much weight loss they might achieve if the drug is used for 12 months. Including patients who drop out lowers the apparent effect of the drug, and fails to give either patient or physician a clear idea of what to expect. We would thus propose using the completers analysis for informing physicians and patients.

Obesity, a chronic medical disease like hypertension or diabetes, has multiple and redundant control mechanisms. It is likely that, as with diabetes and hypertension, multiple medications working by different mechanisms will need to be employed for effective management. Since combinations of drugs have been approved for hypertension and diabetes, this raises the issue of combination therapy in the treatment of obesity, and the criteria for approving such combinations of drugs to treat obesity. The advantages of combination therapy are that lower doses of active medication might be used with fewer side effects,

or that the magnitude of weight loss might be significantly greater. To document these changes, clinical trials comparing active agents would be required after the approval of the parent compound. Strategies for reducing dosages and for increasing the magnitude of the response may require placebo-controlled trials lasting 6 to 12 months. Longer periods might not be needed, since each group would already have been approved with longer trials.

Thank you for the opportunity to respond to your Request for Comments on the Draft Guidance on the Clinical Evaluation of Weight-Control Drugs.

Sincerely yours,

George A. Bray, M.D.
Boyd Professor

Donna H. Ryan, M.D.
Associate Executive Director

Frank L. Greenway, M.D.
Professor, Chief Outpatient Clinic

Steven R. Smith, M.D.
Associate Professor, Chief In-Patient

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03D-0570_emc-000001

From: Robinson, Connie [connie_robinson@merck.com]
Sent: Tuesday, April 20, 2004 3:44 PM
To: 'fdadocket@oc.fda.gov'; Hassall, Thomas
Subject: Docket 2003D-0570 Request for Comments on a Draft Guidance on the Clinical Evaluation on Weight-Controlled Drugs

Attached are the comments of Merck Research Laboratories on Docket 2003D-0570 Request for Comments on a Draft Guidance on the Clinical Evaluation on Weight-Controlled Drugs.

<<Comment Ltr 2003D-0570.pdf>> <<2003D-0570 Obesityfinal2.doc>>

We have provided a pdf file with the signed Merck comments letter; we have also attached a Word file of that letter for your convenience.

Please confirm receipt of these comments, and let us know if there is any difficulty with the files.

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April 20, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Docket No. 2003D-0570 – Request for Comments on a Draft Guidance on the Clinical Evaluation of Weight-Control Drugs

Merck & Co., Inc, is a leading worldwide, human health product company. Merck Research Laboratories (MRL), Merck's research division, is one of the leading U.S. biomedical research organizations. Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment. We believe that FDA's continued effort to provide guidance on the clinical development of health care products encourages and facilitates therapeutic advances.

MRL applauds the FDA for its proactive stance on obesity as a serious and life-threatening disease and the importance of pharmacotherapy for obesity. Obesity is a significant worldwide health problem. It is associated with an increased risk of Type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease, gallstones, osteoarthritis, certain forms of cancer, and an overall reduced life expectancy. It is apparent, therefore, that, beyond the intrinsic value in achieving weight loss, improvement in co-morbid conditions is clearly important.

MRL is pleased to support the effort of the FDA by providing comments on the 1996 draft FDA "Guidance for the Clinical Evaluation of Weight-Control Drugs" as requested in the Federal Register of January 26, 2004.[1] These comments and recommendations are points to consider in the development of a new guidance for anti-obesity drugs. Moreover, MRL encourages the FDA to broaden the scope of the future guidance to provide direction for sponsors on assessment of weight loss and improvements in co-morbid conditions as well as recommendations for the treatment of Metabolic Syndrome, a recently recognized condition associated with a specific clustering of cardiovascular risk factors. The comments below are intended to clarify for sponsors the interpretation of information within the new guidance.

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69 FR 3588, January 26, 2004

GENERAL COMMENTS

The following comments are points to consider from the 1996 draft guidance that MRL recommends be retained in the new guidance document.

1. Patient population

MRL agrees that pharmacotherapy should be considered for obese patients. The definition of obesity in the 1996 draft Guidance for Weight-Control Drugs as individuals with body mass index (BMI) $\geq$30 kg/m^2 and $\geq$27 kg/m^2 with concomitant risk factors is appropriate. This definition of obesity is consistent with the recommendation from the National Heart, Lung and Blood Institute. MRL also recommends that increased waist circumference, as a surrogate for visceral adiposity, be viewed as a concomitant risk factor given its strong correlation with metabolic abnormalities, including insulin resistance, cardiovascular disease, high blood pressure, and lipid abnormalities.

2. Duration of pivotal efficacy studies

Merck supports the proposal that pivotal studies to demonstrate weight loss efficacy for a new drug should be 12 months. However, MRL encourages the FDA to recognize that there may be special circumstances, such as the evaluation of the effects of co-administration (see below) where shorter treatment paradigms could be considered. Sponsors should discuss such situations with the FDA early in a development program.

3. Weight-loss efficacy

MRL concurs that one of two demonstrations of weight loss is appropriate for registration: (1) statistically significant between-group difference in proportion of 5% responders ("5% responders" are those patients who lost $\geq$5% of baseline body weight) *or* (2) statistically significant difference in mean weight loss between placebo and drug treatment.

4. Quality of life benefits

It is generally recognized that obesity negatively impacts individuals' quality of life; therefore, validated patient-reported outcome measures of the impact of obesity and weight loss on quality of life are appropriate in clinical trials to assess the benefits of drug-induced weight loss and weight maintenance. MRL endorses the suggestion in the 1996 Guidance that favorable changes in patient-reported outcomes such as quality of life may be mentioned in labeling.

POINTS TO CONSIDER IN FUTURE GUIDANCE

TRIAL CONSIDERATIONS

1. Duration of placebo run-in duration

The 1996 draft guidance recommends that "patients should not be placed on drug as long as weight loss continues without drug but may be randomized when weight

plateaus". As most obese patients have previously failed to lose weight (or maintain weight loss) after repeated attempts of diet/exercise intervention, MRL considers such a long placebo run-in inappropriate. Furthermore, a variable-length placebo run-in presents special challenges for trial design and data analysis. For these reasons, it is unwise to require that randomization be delayed until weight loss plateaus and is appropriate to consider a shorter, fixed duration run-in period. We propose that a placebo run-in period of 2 weeks duration is adequate.

2. Methods to assess weight maintenance

The original draft guidance suggests that maintenance of weight loss may be the principal benefit of anti-obesity therapy. Further clarification on the design of studies to demonstrate weight maintenance should be detailed in the future guidance. MRL suggests three possible treatment paradigms could be used to assess weight maintenance: (1) weight maintenance after drug-induced weight loss, (2) weight maintenance after diet-induced weight loss (e.g. 6 weeks of a very low calorie diet) *or* (3) prevention of weight gain associated with use of certain medications (e.g., sulfonylurea, anti-psychotics, anti-epileptics, corticosteroids, etc.) or therapies (e.g., smoking cessation). In the first two paradigms, it should be possible to demonstrate the efficacy of drug-treatment to reduce body weight regain (or further decrease body weight) in studies of one year duration or less. Sponsors should assess the between-group difference in proportion of patients who maintain a clinically meaningful degree of weight loss (e.g., 5% of baseline body weight). For the third paradigm, it should be possible to demonstrate efficacy by establishing a statistical difference in weight gain between the drug- and placebo-treated groups in studies lasting one year or less.

3. Methods to assess improvements in obesity associated co-morbidities

Measurement of obesity-associated co-morbidity endpoints (lipids, blood pressure, and glucose tolerance) is encouraged in the 1996 draft guidance. MRL proposes the following metrics to assess the effectiveness of weight control drugs on obesity associated co-morbidities: (1) improvements in lipids, blood pressure, and/or fasting plasma glucose *or* (2) proportion of patients with a reduction in the dose of medication(s) used to treat co-morbid condition(s) (e.g., lipid-lowering therapy, anti-hypertensive therapy, and/or glucose-lowering therapy). Effects on any of the obesity-associated co-morbidities should be described in the label without regard to multiplicity.

4. Methods to assess Metabolic Syndrome

MRL encourages the FDA to consider the inclusion of patients who meet the criteria for the Metabolic Syndrome. The National Cholesterol Education Program Adult Treatment Panel III report defined metabolic syndrome as the presence of any 3 of the following 5 risk factors: abdominal obesity, elevated triglycerides, decreased HDL, increased blood pressure, or impaired fasting glucose.

MRL suggests that a treatment-related decrease in the proportion of patients satisfying the criteria for the metabolic syndrome could be used to support an indication for *Management of Metabolic Syndrome*.

5. Life-style modification

It is appropriate to recommend life-style modification, including a modestly restricted diet and regular exercise during clinical studies. However, it should be possible to conduct studies with variations of the components of life-style modification (e.g., no caloric restriction or caloric restriction applied only to one or more macronutrient components of the diet).

6. Safety data

The 1996 draft guidance specifies that safety of weight control drugs for long-term administration must be demonstrated in 1500 subjects for 12 months and 200-500 subjects for 24 months. These numbers greatly exceed the ICH-E1A (*Guideline for Industry: The extent of population exposure to assess clinical safety*). This ICH guideline specifies that 1500 subjects should be exposed to short-term exposure to drug, 300-600 patients for 6 months and 100 patients for a minimum of 1 year. MRL proposes the updated FDA guidance for obesity should reflect the patient exposure recommendations in ICH-E1A.

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MRL believes that FDA's guidance should recognize the difficulties of patient retention in obesity clinical trials. Missing data is endemic to obesity clinical trials, which makes interpreting results very difficult. MRL recommends that study reports should characterize the extent of missing data and sensitivity analyses should be performed to assess the impact of the missing data. In addition, FDA should accept the use of alternatives to carrying forward the last observation (LOCF) for the primary statistical analysis.

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Given the modest efficacy of the currently marketed anti-obesity therapies, there will be interest from physicians and patients to explore co-administration of existing agents with new therapies having different mechanisms of action. MRL believes that a single study is sufficient to support a co-administration indication. The study duration should be at least 6 months, unless one of the agents is indicated for short term use. Preclinical safety studies, beyond those for registration of the individual agents,

should not be necessary unless there is reason to anticipate a pharmacokinetic or pharmacodynamic interaction. In certain circumstances it may be necessary to discuss available safety data with the agency. Sponsors should be encouraged to discuss with FDA co-administration of novel therapies.

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The existing guidance acknowledges that maintenance of prior weight loss (or prevention of weight regain) may be an important goal of drug therapy. Therefore, the future guidance should include the necessary information to enable sponsors to pursue stand-alone indications for weight maintenance and/or prevention of weight gain. MRL proposes that two independent studies (demonstrating statistically significant between-group differences) are sufficient to support registration for a stand-alone indication. Sponsors can rely on a single study for weight maintenance if it is part of a comprehensive weight loss/weight maintenance development program.

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Given the association of Metabolic Syndrome with obesity, and the clear link with increased cardiovascular morbidity and mortality, MRL proposes that FDA consider an indication for this syndrome.

ADDITIONAL CONSIDERATIONS FOR FUTURE GUIDANCE

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Many anti-obesity agents are centrally-acting anorectics which may require assessment of abuse liability potential [21CFR 314.50(c)(5)(vii)]. MRL requests that a distinction be made in the future guidance between misuse (e.g. weight loss in non-obese subjects) and abuse (e.g., unintended use of product). The absence of clear guidance for the assessment of abuse liability may hamper progress in the development of novel therapeutic agents. Therefore, MRL encourages the FDA to issue the pending guidance on Assessment of Abuse Potential of Drugs or provide specific direction to Sponsors on the preclinical/clinical studies required to assess abuse liability.

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Obesity is now recognized in the US as a serious and life-threatening disease. MRL proposes that FDA consider weight loss drugs as eligible for accelerated approval programs including Fast Track. In addition, MRL recommends that the new guidance include specific directives on the eligibility for Fast Track review and accelerated approval for weight loss products.

We welcome the opportunity to comment on this guidance and, if appropriate, to meet with you to discuss these issues.

Sincerely,

for Donald Black, MD
Vice President, Global Regulatory Policy

April 20, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

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We welcome the opportunity to comment on this guidance and, if appropriate, to meet with you to discuss these issues.

Sincerely,

Donald Black, MD
Vice President, Global Regulatory Policy

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Lilly

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April 21, 2004

Dockets Management Branch (HFA - 305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket Number 2003D-0570
Request for Comments on: 1996 Draft Guidance for Industry on the Clinical Evaluation of Weight-Control Drugs.

Eli Lilly and Company (Lilly), as a global research based pharmaceutical company, is committed to the development of innovative medications for the treatment of obesity.

The obesity epidemic is a pervasive health problem in the United States. Obesity in the United States has increased steadily since the 1980s. From 1988 through 1992, fewer than 56 percent of American adults were overweight and fewer than 23 percent were obese; however, today over 64 percent are overweight and over 30 percent are obese (Flegal et al., 2002; Working Group on Obesity, 2004). This epidemic is not confined to adults. Data published by the Centers for Disease Control and Prevention (CDC) in 2003 demonstrates that 15 percent of children and adolescence ages 6 through 19 are overweight, which is double the percentage of two decades ago (cited in Working Group on Obesity, 2004). As Americans become heavier, their health suffers. Overweight and obesity increase the risks of other diseases such as type 2 diabetes, coronary heart disease, and certain cancers. According to some estimates, at least 400,000 deaths annually may be attributed to obesity (Mokdad, et al., 2004).

Lilly congratulates the FDA on its initiative described in the 11-February-04 Report of the Working Group on Obesity to aggressively address this pervasive, important health problem. In particular, Lilly is encouraged by the FDA's plan to revise the 1996 draft guidance cited above and appreciates the opportunity to comment. Lilly participated in the April 2003 and March 2004 meetings, hosted by the American Obesity Association (AOA), that provided opportunity for the AOA-industry representatives to discuss with FDA suggested changes to the draft guidance. Prior to the March 2004 meeting, AOA submitted to FDA a revision of the 1996 draft guidance that addressed issues for which there was general agreement among the AOA-industry participants on the need for change. Lilly supports AOA's revision and offers additional comments below as they relate to each of the six major sections of the AOA revision.

2003D-0570 C3

GUIDANCE FOR THE CLINICAL EVALUATION OF DRUGS FOR THE TREATMENT OF OVERWEIGHT AND OBESITY

1. INTRODUCTION

Obesity is a Disease: Obesity is a chronic metabolic disease characterized by excess adiposity and associated with significant morbidity and mortality due to the complications of the cardiovascular, metabolic and other organ systems. Treatment of obesity is directed at a reduction in excess adiposity and its associated risks. One should be sure to consistently use the proper terminology of "drugs for the treatment of obesity" which effectively identifies obesity as a disease and the objective of drug therapy as treatment of the disease. Archaic terminology, such as "weight-control drugs" which diminishes the importance of obesity as a health hazard, or the significance of the role of drug therapy, should be abandoned. In addition, correctly identifying obesity as a disease with significant morbidity and mortality (Working Group on Obesity, 2004) will facilitate patient access to effective therapy by reducing barriers for healthcare reimbursement. Currently, many healthcare plans do not provide reimbursement for treatment for obesity because it is not recognized as a disease. Facilitation of patient access to therapy for obesity will become more important in the next decade because of the anticipated development of more effective drugs.

Different Mechanisms for Treatment of Obesity and the Need for Flexibility: The current FDA draft guidance is reasonably well suited to the development of monotherapy for the treatment of obesity that are similar in mechanism, efficacy and potential risk to previously approved drug therapies. Currently approved drug monotherapies are limited in efficacy. Major breakthroughs can occur either by drugs aimed at novel targets or by combination therapy. As new scientific discoveries increase our understanding of the pathogenesis of obesity, its associated risks, and in potential treatment targets, this is an ideal opportunity to create a guidance which describes sound development principles and meaningful guidance without being excessively prescriptive or which narrowly address issues observed with previously approved drugs. The guidance should be forward-looking and flexible enough to facilitate the development of the broad range of pharmacotherapies, including combination therapies, that can be expected over the next decade, and beyond. The new guidance need not be limited by the assumptions that future treatments will be similar in any way to previously approved drugs.

2. GENERAL RATIONALE

Definitions of the Disease are Evolving: Excess adiposity presents a continuum of cardiovascular, metabolic and other risks to the patient, even with degrees of excess adiposity well below the currently used diagnostic BMI criteria (>30 kg/m2). This is particularly true for the risk of diabetes, for which the increased risk of excess adiposity begins even at BMI considered normal (<25 kg/m2) (Kopelman, 2000). Therefore, although widely used, the conventional classification of normal, overweight, obese and morbidly obese is somewhat arbitrary. The currently used BMI diagnostics criteria is not necessarily applicable to ethnic populations such as native Americans or Asians (Tanchoco et al., 2003), nor does it account for the risks of visceral adiposity, even at modest degrees of obesity. As knowledge of obesity and drug treatments of obesity evolves, it is likely that the currently described BMI criteria (>30 kg/m2 without comorbidities or >27 kg/m2 with comorbidities) will evolve, just as the diagnostic criteria and treatment goals for other chronic metabolic diseases such as hypertension, diabetes, and hyperlipidemia have evolved over the past 20 years. Although the current BMI criteria is a reasonable starting place for most

studies of occidental Caucasian populations, the guidance should anticipate the evolution in understanding of obesity and allow sponsors to choose criteria for inclusion in studies are based on the current knowledge of the relationship between risk and excess adiposity. Such criteria may not necessarily be based solely on body weight or BMI, but may also include waist circumference, other anthropomorphic measurements, or other assessments of excess adiposity that have been shown to be associated with excess risk.

3. POPULATION

Effect of Excess Adiposity on Different Populations: As described above, the diagnostic criteria for the study populations should be based on the risk associated with excess adiposity. While the BMI criteria of >30 kg/m2 without comorbidities or >27 kg/m2 with comorbidities is suitable for most studies of occidental Caucasian populations, there may be specific populations with lower BMI which are appropriate populations due increased risk of morbidity, such as Asian populations or populations with predominantly visceral adiposity (Tanchoco et al., 2003)

Childhood and Adolescent Obesity: Obesity in childhood and adolescence is emerging as an important public health issue. Diagnostic criteria and the role of pharmacotherapy will may be different in pediatric and adolescent populations still in an active growth and weight gain phase than in an adult population. Because of the increasing numbers of adolescents with obesity, sponsors should be encouraged to include studies of this patient population in their clinical development plan. Although specific guidance for the study of pediatric populations is beyond the scope of this guidance document, sponsors should be encouraged to include plans for addressing this growing public health concern in individual discussions with the Agency.

Population Diversity: Phase 3 studies should include diverse populations. Due to the smaller sizes and different objectives of Phase 1 and 2 studies, diverse populations should not be required in early development unless driven by a specific need (for example if the drug is metabolized by an enzyme known to have significant ethic differences.)

4. PHASE 1 STUDIES

There are no unique aspects to Phase 1 studies of obesity treatments. This could be stated explicitly or this section deleted altogether. Sponsors should be encouraged to develop and use biomarkers for the early assessment of potential efficacy and to guide the selection of dose regimens for subsequent stages of drug development.

5. PHASE 2 STUDIES

There are no unique requirements for Phase 2 studies in the development of drugs for the treatment of obesity. The size, duration and population studied should be sufficient to support the design and dose selection for the Phase 3 studies. A specific study design cannot be prescribed as it will differ based on the rapidity of onset of the drug effect, the availability of one or more biomarkers, and the design of the subsequent Phase 3 study. For example, if a sponsor intends to include 3 active doses in Phase 3 studies of a rapidly acting compound with a good biomarker for efficacy, the Phase 2 study may only need to be large enough and long enough to define the no-effect dose based on the biomarker and to assure tolerability of the higher doses with chronic administration. On the other hand, if the sponsor intends to include only a single dose of a more slowly acting drug without a good efficacy

biomarker in Phase 3, the Phase 2 studies should be substantially larger and longer to assure that the dose selected for Phase 3 has the optimum benefit-risk characteristics.

6. PHASE 3 TRIALS

Trials to establish the safety and efficacy of a drug for the treatment of overweight and obesity should be randomized, double-blind, and placebo-controlled. Other interventions, such as dietary and activity regimens should be balanced across treatment groups. The total size of the exposed population required to demonstrate safety should be driven by specific objectives or safety issues. ICH guidelines describe the rational basis for safety exposure required by ICH and seem suitable for chronic use treatments for obesity. The current FDA draft requires size and duration of safety exposure far in excess of ICH requirements; however, it does not provide the rationale for such a requirement. While individual drugs may require safety exposure which is larger or longer than ICH guidelines if data from nonclinical toxicology studies or previous experience with similar drugs suggests an important potential safety issue which is known to be rare or significantly delayed in onset, it is not rational to impose this requirement on all drugs.

6.1 ENDPOINT EVALUATION

Weight Loss as a Surrogate of Loss of Fat: The objective of a treatment for obesity is reduction of excess adipose tissue and its associated risks. Accurate and precise direct measurement of adipose tissue is currently impossible or impractical in large Phase 3 studies. In most cases, weight can be established by an appropriate surrogate in Phase 2 or 3 by the use of body composition measurements in an appropriately designed study. If weight loss is shown to be appropriate surrogate for fat loss, it is not necessary to directly measure fat mass or body composition in every Phase 3 study. Actual weight loss should be reported. It is helpful to express weight loss in relative terms such as percent of body weight or percent of excess over ideal body weight or change in body mass index. For drugs that reduce visceral adiposity, another surrogate measure, such as waist circumference or mid-sagittal diameter, needs to be established as an appropriate endpoint for implementation in Phase 3.

In studies in which weight loss is the primary objective, the currently described requirements for statistically significant 5% decrease compared with placebo or statistically significant increase in the proportion of patients who achieve 5% weight loss compared to placebo remains appropriate. In addition, analyses of proportions of patients which achieve 10% or 15% weight loss would be important information.
In studies in which maintenance of weight loss or prevention of weight gain is the primary objective, the drug should show statistically significantly greater proportion of patients who maintain at least a 5% weight loss.

Reduction in Visceral Adiposity: For drugs which have primary effects on reducing visceral adiposity or which may enhance lean body mass in addition to reducing adipose mass, body weight loss may substantially underestimate the therapeutic effects of the drug, and the above criteria may not be appropriate measures of efficacy. In these cases, another valid endpoint will need to established by the sponsor and agreed upon by the Agency prior to use in Phase 3 studies. For example, reduction in visceral adiposity could be established by reduction in waist circumference, by imaging methods, or by showing improvements in metabolic markers of visceral adiposity, such as reductions in serum lipids, blood pressure, serum C-reactive protein, or serum leptin, or increase in serum adiponectin. The combination of favorable improvements in metabolic markers should be taken as a whole,

and individual markers should not necessarily be expected to be as great as one would expect for a specific indications such as hypertesion or hyperlipidema.

Diet Run-In as Part of Study Design: The inclusion and duration of a diet run-in phase may depend on the objectives of the Phase 3 study. As most adults seeking medical treatment for obesity have already failed non-pharmacological treatment on multiple occasions, it is unnecessary to demonstrate within the course of the study that dietary intervention will fail to normalize body mass. At the most, an elicited history of failed dietary intervention should be sufficient. In all studies, the total weight loss from baseline includes the effect of drug and non-drug interventions, and the estimate of drug effect is obtained by comparing the drug treatment arms to placebo arms. In those studies in which a dietary or other intervention is included in the regimen prior to instituting drug therapy, weight loss from baseline should also be assessed from the beginning of the total regimen, not just from the start of drug treatment, and the estimate of drug effect is likewise derived from the comparison to placebo.

As our knowledge of obesity advance, it may be possible to identify patients who will not respond well to drug treatment. Whether they are identified by failure to respond to a diet run-in or by some biochemical marker, if entry into Phase 3 studies excludes patients who are not expected to respond, the same limitation should be reflected in the product label.

Obesity-Associated Cardiovascular and Metabolic Risk Factors: The protocol and analysis plans should describe the obesity-associated cardiovascular and metabolic risk factors (e.g., lipids, blood pressure and glucose tolerance) that would be measured; and the results of those analyses, whether positive, neutral, or negative, should be described in the label. It should not be necessary to show that the improvements in risk factors are independent of weight loss, as weight loss is the mechanism by which the risk factors are improved, and it is important for physicians and patients to understand the cardiovascular and metabolic effects of weight loss.

6.2 DURATION OF TRIALS

Obesity is a chronic metabolic disease; therefore, the duration of treatment should be sufficient to demonstrate efficacy and safety with chronic dosing, with initial trends established within the first 6 months and durability established with a primary endpoint at one year. Although the treatment of obesity requires demonstration of long-term weight loss, it is likely that drugs will be developed which are most useful in the induction of weight loss, after which a different weight maintenance regimen (either pharmacological or non-pharmacological) is instituted. In this case, even though the drug treatment induction may be relatively short (perhaps 3-6 months), the primary endpoint must still be at one-year, demonstrating the long-term benefit of the initial drug treatment.

Sincerely,

ELI LILLY AND COMPANY

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April 23, 2004

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Re: Comments on Draft Guidance for Industry on the Clinical Evaluation of Weight-Control Drugs - Docket No. 2003D-0570 (Federal Register Notice 26 January 2004 [Vol. 69, No. 16])

Dear Sir or Madam::

GlaxoSmithKline (GSK) supports the Food and Drug Administration's (FDA's) initiative to facilitate development and availability of innovative medical products by updating its 1996 Draft Guidance for Industry entitled, *"Guidance for the Clinical Evaluation of Weight-Control Drugs."* In response to FDA's solicitation for public input prior to republication of the guidance as a draft, this submission provides the collective response on behalf of GlaxoSmithKline (GSK).

Since the Agency issued the draft guidance on September 24, 1996, overweight and obesity have become more readily recognized as a disease that is associated with morbidity and early death. In a recently published paper in *JAMA* (2004; 291:1238-1245), poor diet and physical inactivity accounted for 400,000 deaths (16.6%) in United States in the year 2000. This is second only to smoking, the current leading cause of death (435,000 deaths; 18.1%). Based on current trends, it is estimated that that poor diet and physical inactivity will soon overtake tobacco as the leading cause of death. These statistics underscore the urgent need to more adequately address the growing epidemic of overweight and obesity in this country. For millions of Americans, efforts to promote lifestyle modification as the primary means to a healthy weight have failed. For these individuals, there is a significant unmet medical need for safe and effective pharmacological treatment options. We acknowledge the efforts of the FDA's Obesity Working Group to address the major public health problem of obesity through its ongoing collaborative activities involving scientific experts from organizations such as the American Obesity Association (AOA), National Institutes of Health (NIH), and the pharmaceutical industry.

In the attached document, we have made a number of proposed specific changes to FDA's 1996 draft guidance. Provided on the following pages, is an overview of some key elements of the changes we have included in GSK's proposal for an updated guidance.

2003D-0570 C4

Key Elements

Lines 1 - 2

We recommend a modification in the title of the guidance to read, "*Guidance for the Clinical Evaluation of Drugs for the Treatment of Overweight and Obesity.*"

Lines 18 - 58

Section 2, General Rationale. Since the initial release of the draft guidance in 1996, there has been a significant body of literature published on the deleterious effects associated with excess weight (i.e., overweight and obesity). Excess weight has now become an alarming epidemic in both the adult and pediatric populations and may soon become the leading cause of mortality. As such, we feel that it is important to more accurately reflect excess weight as a disease and acknowledge the multifactorial nature of its etiology. We have provided suggested language to reflect the severity of this burden and have stressed the importance of being able to provide pharmacological treatment options. Examples also have been provided as to how overweight and obesity can be measured, and acknowledgment has been made that certain groups have increased health risks at the currently accepted body mass index (BMI) definitions for overweight and obesity.

Lines 59 - 79

Section 3, Potential Therapeutic Indications. Because overweight and obesity are affected by a variety of contributing factors, we suggest that the guidance identify a range of possible clinically meaningful benefits of drugs to treat excess weight, including the following indications, which will be discussed in greater detail in subsequent sections of the document:

1. Reduction in weight (i.e., percentage weight loss)
2. Improvement in body-fat composition (i.e., reduction in the proportion of adipose tissue)
3. Sustained weight reduction (i.e., weight-loss maintenance / prevention of regain)
4. Prevention of weight gain associated with other effects (e.g., occurring with use of certain medications or during smoking cessation)

Lines 80 - 103

Section 4, Population. We believe that for the intended use, the guidance should encourage the assessment of the drug in an appropriately diverse patient population (demographics, concomitant drug use, etc.).

In recognition of the significant public health threat to children and adolescents, the guidance should encourage initiation of pediatric studies as early as practicable, when a therapeutic benefit is anticipated. The guidance, however, should not include any requirements for pediatric data that might delay the availability important new treatments for adults.

We feel that sponsors should be able to define the study population in support of a specific, desired indication. If a sponsor chooses to pursue an indication in patients who fall outside of the recommended BMI attributes (e.g., ethnic groups who may be at higher risk at lower BMIs) or places a focus on specific subpopulations, an appropriate justification should be provided and agreement reached with the Agency. We believe that the primary goal should be to make new treatment options available as soon as possible to those who can most benefit. As such, the Agency should not require evaluation of a new drug in all possible patient groups prior to initial approval. The sponsor should provide justification for the specific population(s) it has targeted for the intended use. If necessary, a description of measures that sponsors would take to facilitate the intended use of the drug may be requested.

We recommend a change in Line 77 of the original draft guidance from "Methods used to recruit subjects for obesity drug trial should be noted" to "Inclusion and exclusion criteria for enrolling subjects for obesity trial should be noted to support the indicated population."

Lines 104 - 112

Section 5, Phase 1 Studies. We recommend that this section be renamed from the previous heading, "Early Clinical Trials" to "Phase 1 Studies." We have maintained the spirit of the original wording in this section, which provides a brief description of the purpose of these studies (e.g., safety, tolerability, and possible pharmacodynamic profiling). A recommendation is made to conduct such studies as randomized, double blind and placebo controlled, but the recommendation should not preclude the sponsor from conducting open-label or single-blind studies.

Lines 113 - 125

Section 6, Phase 2 Studies. We recommend that this section be renamed from the previous heading, "Dose Range Finding" to "Phase 2 Studies." Likewise, we have maintained the spirit of the original wording in this section, which provides a brief description of the purpose of these studies (e.g., safety, efficacy, and dose-response evaluation in the target population). Because there are numerous means by which to provide dietary and activity regimens, we believe that the guidance should not be restrictive in these areas. We have thus recommended that standardized dietary and activity regimens should be provided, as appropriate for the indicated patient population, within a trial. This will permit a sponsor to design the clinical trial with greater flexibility in regard to inclusion of the type of lifestyle modification as well as to provide a holistic approach for the study participant.

Lines 126 - 146

Section 7, Phase 3 Studies. We recommend that this section be renamed from the previous heading, "Trials to Establish Efficacy" to "Phase 3 Studies." Although the general spirit of the original wording within this section and its subsections has been maintained, we believe that there should be no inclusion of a run-in period, because this does not always reflect the real-world situation, and it may confound the interpretation of data. We advocate an holistic approach by providing an accompanying standardized lifestyle modification

within a given trial that would suit the desired indicated population. We have provided suggested wording to encourage evaluation of diverse populations for the intended use (e.g. demographics, concomitant diseases, etc). The population should be defined to support a given indication / claim, and, if so desired, a sponsor could also include an active control.

Lines 147 - 208

Section 7.1, Endpoint Evaluation. Because overweight and obesity are affected by a variety of contributing factors, we suggest that the guidance identify a range of possible clinically meaningful benefits of drugs to treat excess weight. In addition, as new agents become available, there is the potential to add onto pre-existing therapy or to use two agents together as an initial approach to weight control, especially if the pharmacological mechanisms of action are complementary. The design for the respective treatment approaches could potentially differ, and the sponsor is encouraged to consult the Reviewing Division on the proposed clinical study design to support any or all of the following indications / claims:

1. **Reduction in weight (i.e., percent weight loss); Section 7.1.1** Lines 155 - 168; We concur with the draft guidance's original criteria for approval.

2. **Improvement in body-fat composition (i.e., reduction in the proportion of adipose tissue); Section 7.1.2**, Lines 169 - 175. Because a favorable change in body composition may not necessarily be accompanied by a decrease in weight (sometimes there may be an increase due to an increase n muscle mass) we believe that a sponsor could also seek approval based on a favorable change in body-fat composition. At this time, however, we cannot recommend quantitative recommendations, but these could be developed, with appropriate input provided from scientific experts via a public consensus meeting.

3. **Sustained weight reduction (i.e., weight-loss maintenance / prevention of regain); Section 7.1.3**, Lines 176 - 186. We feel that a sponsor could also obtain an indication based on the demonstration of maintenance of prior weight loss / prevention of the weight regain. This demonstration can be independent from having to demonstrate weight loss with the same therapy. The means by which weight loss had been achieved, however, must be standardized within a given study (e.g., responders on prior drug therapy [monotherapy or combination therapy] or responders on a specified weight-loss program, such as Weight Watchers).

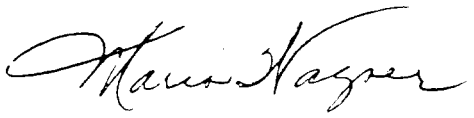
4. **Prevention of weight gain associated with other effects (e.g., occurring with use of certain medications or during smoking cessation); Section 7.1.4**, Lines 187 - 191. We believe that there are certain populations that may become more susceptible to weight gain and, as such, as sponsor could obtain approval based on the prevention of weight gain in such populations.

Lines 192 - 208	**Additional Endpoints for Evaluation.** We advocate the Agency's previous recommendations to measure additional endpoints (e.g., HbA1c, blood pressure, lipids, etc). Although we believe the information should be included in the drug's labeling, it is not intended to convey a separate indication. These data provide important considerations for benefit-risk decisions when prescribers/patients assess potential treatment options. We also encourage a sponsor to assess patient-reported outcomes (e.g., quality of life, patient satisfaction and patient preferences, among others).
Lines 209 - 224	**Section 6.2, Duration of Trials.** The updated *Guidance for the Clinical Evaluation of Weight-Control Drugs* should reflect similar considerations for safety and efficacy assessments included in Guidance for other chronic conditions (e.g. Type 2 DM, dyslipidemia, and hypertension). For such conditions, the adequacy of the submission database should depend largely on the efficacy attainable and absence of unacceptable risks, within the context of unmet medical need. We believe that the duration of a trial should support the primary efficacy endpoint and the drug's intended use. Drugs intended to address weight-related endpoints should not be held to a higher standard than those approved for other disease states. For approval, we recommend that the trials be of 12 months in duration. Although we agree with the Agency's previous recommendation that the safety population include at least 1500 subjects completing 12 months of study, we do not agree that 24 months of safety data should be required in at least 200-500 patients prior to approval. If considered necessary, however, a sponsor's commitment to collect long-term safety post-approval under actual clinical use conditions may be required as part of a formal product surveillance program.

In addition to the input provided in this submission, we also want to acknowledge that GSK representatives, along with other members of industry, FDA and NIH have participated in recent discussions sponsored by AOA regarding the effort to update the guidance. We note that AOA's comments were submitted to the docket 8 March 2004. GSK has also contributed comments to PhRMA as it developed its response to FDA. Although there may be some specific differences in some of the recommendations, in general, we support the recommendations submitted by AOA and PhRMA.

We appreciate the opportunity to provide our input and look forward to the Agency's continued efforts to facilitate development of safe and effective treatment options to address the significant health threat posed by overweight and obesity.

Sincerely,



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GUIDANCE FOR THE CLINICAL EVALUATION OF DRUGS FOR THE TREATMENT OF OVERWEIGHT AND OBESITY

1. INTRODUCTION

This guidance is intended to recommend clinical trials and clinical drug development programs that will provide acceptable demonstrations of the safety and efficacy of drugs to treat overweight and obesity. General guidelines for conduct of clinical trials and for development of new drugs for marketing should be followed in developing such drugs. Only those aspects of the trials that are specific to such drugs will be discussed in this document. Refer particularly to the Guidelines for the Format and Content of the Clinical and Statistical Sections of New Drug Applications.

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

2. GENERAL RATIONALE

Obesity is a long-term, chronic, and relapsing disease in which the principal sign is excess adipose tissue resulting from imbalance in energy expenditure and energy intake. It is a multifactorial disease in which gender, race, genetic, metabolic, environmental and behavioral factors can contribute, and it is affected by powerful neuroendocrine factors that affect both hunger and satiety. Excess weight alone causes a number of changes in the body's lipids and hormonal activity, and obesity significantly affects the musculoskeletal and cardiovascular systems. Obesity is associated with significant morbidity and premature death, and it has become a serious public health problem in the United States, reaching epidemic proportions in adults, children, as well as the elderly. Over 25% of adult Americans are obese, and the percentage of obese can be much higher

in some subpopulations. The adult population with morbid or severe obesity (approximately 100 pounds overweight or a Body Mass Index [BMI] > 40) is nearly 9 million persons.

Obesity is well established as a cause of many important comorbid conditions, including some cancers, stroke, heart disease, hypertension, hypercholesterolemia, osteoarthritis of the knee and hip, and type 2 diabetes. In addition, obesity is strongly associated with other adverse health conditions such as gall bladder disease, sleep apnea, depression and low self-esteem. Lack of physical activity and poor nutrition account for approximately 400,000 deaths each year, making these risk factors currently second only to tobacco use in causes of preventable death (CDC Study, *Actual Causes of Death in the United States, 2000; JAMA* (2004) 291:1238-1245). Extrapolation of these data suggest that the lack of physical activity and poor nutrition will likely surpass tobacco use as the number one cause of preventable death. With the rising rate of obesity and the resulting consequences for chronic conditions and potentially death, it is a public health imperative to develop effective measures to help patients maintain a healthy weight. For those patients for whom appropriate nutrition and behavioral changes have proven ineffective, there is a significant unmet medical need for safe and effective medications. Development of pharmacological treatment options is a critical priority as part of an innovative approach to helping Americans achieve a healthy weight.

Obesity may be measured in several acceptable ways. Surrogate measures include excess pounds over a healthy weight, waist circumference, BMI, or waist-to-hip ratio. The National Institutes of Health, the Centers for Disease Control and Prevention and the World Health Organization have used the BMI scale. According to generally accepted cutoff points, the BMI for overweight is defined as equal to or greater than 25 to 29.9, obesity as 30 to 39.9 and severe or morbid obesity as 40 or greater. There are some select populations (e.g., Asian), however, that have been shown to have increased health risks associated with overweight / obesity at lower BMI values. BMI does not distinguish size that is due to bone and muscle from that due to fat, nor does it identify subjects with visceral obesity, a potent predictor of morbidity. Drug developers may use any scientifically acceptable measurement definition.

3. POTENTIAL THERAPEUTIC INDICATIONS

Obesity is a complex, multifactorial disease that may differ among individuals based on race, ethnicity, genetic difference, or other underlying disorders, and may differ in a given individual across time. In addition, current research indicates that there are distinct physiological systems that contribute to weight loss, weight maintenance and weight gain. Therefore, a therapeutic regimen that might affect one or more of these systems could be considered for registration. Ideally, a successful therapeutic regimen for patients could potentially include any or all of the following indications:

1. Reduction in weight (i.e., percent weight loss)
2. Improvement in body-fat composition (i.e., reduction in the proportion of adipose tissue)
3. Sustained weight reduction (i.e., weight-loss maintenance / prevention of regain)
4. Prevention of weight gain associated with other effects (e.g., occurring with use of certain medications or during smoking cessation)

To achieve one or more of the aforementioned goals, single drugs or drugs in combination may act on one or more mechanisms that affect excess adiposity. These may include reduction of hunger/appetite, enhancement of satiety, alteration in food preferences, enhancement of physical activity, increases in energy expenditure or enhancement of fat oxidation. In addition to the known mechanisms of increased adiposity listed above, a drug may be targeted at novel mechanisms or strategies that at this time are unknown.

4. POPULATION

The supporting clinical program for a potential new drug for treatment of overweight and obesity should include a diverse patient population. Accordingly, within the intended use population, only patients with obvious contraindications should be excluded from Phase 3-study entry. Inclusion of diverse populations would allow for the collection of safety data in important demographic groups such as the elderly, appropriate pediatric populations, patients with concomitant diseases, or patients taking common concomitant

medications. Study activities should ensure collection of all pertinent demographic information.

Because obesity is a significant public health threat to children and adolescents, when a therapeutic benefit in pediatrics is anticipated, initiation of studies should be initiated as early as practicable.

For most overweight and obesity drug studies, subjects in clinical trials should have a body mass index (BMI) of at least 30 for otherwise healthy individuals, and BMI at least 27 for those with comorbid conditions (such as, hypertension, hyperlipidemia, glucose intolerance, cardiovascular disease, sleep apnea, or other obesity-related conditions). It is often preferable to identify obesity by methods that measure body fat and its distribution. Inclusion and exclusion criteria for enrolling subjects for obesity trial should appropriate for the targeted population.

Drugs that effectively address weight control in overweight patients with a BMI in the range of 25 to 27 may provide a meaningful therapeutic benefit, particularly in those demographic subgroups at increased risk of morbidity. Specific plans to include patients with a BMI in the range of 25 to 27 should be described and justified as part of End of Phase 2 discussions.

5. PHASE 1 STUDIES

For new chemical entities, the earliest clinical trials for safety, tolerability, and pharmacokinetic profiling are usually performed in subjects who are otherwise free of disease. In some instances, pharmacodynamic profiling and dose determination also may be possible.

In order to discern adverse effects due to study drug, it is recommended that studies be randomized, double blind and placebo controlled. This does not preclude, however, the conduct of either open-label or single-blind studies; conduct of such studies are at the sponsor's discretion.

6. PHASE 2 STUDIES

Phase 2 trials should be designed to obtain guidance for the design of Phase 3 trials. The goals of Phase 2 studies are to capture information on safety, efficacy and dose response in the target population. The studies should obtain working estimates of the nature and severity of side effects commonly associated with the new product. They should also include a parallel dose-response study across a number of dose levels sufficient for the initial characterization of the dose-response curve for the drug. Patient history may include a number of factors, including family history, alcohol intake, tobacco use, exercise/activity level, dietary habits, comorbidities and concomitantly administered drugs. Dietary and activity regimens should be defined and standardized within a trial and as appropriate for the patient population. Trials should usually be randomized, double blind, and placebo controlled. They should be of sufficient duration to demonstrate preliminary evidence of efficacy and safety.

7. PHASE 3 STUDIES

Trials to establish the safety and efficacy of a drug for the treatment of overweight and obesity should be randomized, double blind, and placebo controlled. Using a range of doses in phase 3 trials could better characterize the relationship between exposure and the resulting clinical benefit and risk, allowing provision of the best dosing advice. In addition, exposure-response data from clinical trials could provide critical information on the need for dose-adjustments in special populations.

To the extent possible, trials should be designed to allow diversity within the target population (e.g., demographics, concomitant illness, co-administered drugs, etc.), and only those patients with obvious contraindications would be excluded from Phase 3 studies. Dietary and activity regimens should be defined and standardized within a trial.

Weight loss achieved with calorie restriction alone is usually associated with loss of both fat and muscle tissue. Exercise has been reported to reduce or eliminate muscle loss. A carbohydrate-restricted regimen will usually result in loss of body water. For these

reasons, it may be desirable in a suitable number of patients, to establish that the subjects have excess body fat by one or more of the accepted measurements, such as skin fold thickness, body circumferences or sagital diameter, under-water weighing, bioelectric impedance, and DEXA. Such approaches can be used in a subset of the population in the Phase 3 program or perhaps in smaller, pharmacodynamic studies. Follow-up measurements can then confirm if body fat is decreased, commensurate with the weight loss, and that weight loss is not associated with excessive loss of body water or muscle.

7.1 Endpoint Evaluation

In addition to monotherapy, as new agents become available, there is the potential to add onto pre-existing therapy or to use two agents together as an initial approach to weight control, especially if the pharmacological mechanisms of action are complementary. The design for the respective treatment approaches could potentially differ, and the sponsor is encouraged to consult the Reviewing Division on the proposed clinical study design to support any or all of the following indications / claims:

7.1.1 Reduction in Weight (i.e., percent weight loss)

To obtain a monotherapy weight-loss indication, the sponsor should demonstrate at least one of the two following criteria:

- The drug effect is statistically significantly greater than the placebo effect, and the mean drug-associated weight loss exceeds the mean placebo weight loss by at least 5%, at the end of one year.

or

- The proportion of subjects who reach a loss of at least 5% of their initial body weight is statistically significantly greater in subjects on drug than those on placebo, at the end of one year.

To obtain a combination therapy indication for weight loss, either as initial therapy or as add-on therapy for patients who would benefit from additional weight loss, the sponsor

should show that the combination provides additional clinical benefit over the individual components and does not result in an unsatisfactory benefit-risk balance.

7.1.2 Improvement in Body-Fat Composition (i.e., reduction in the proportion of adipose tissue)

For monotherapy, the two criteria outlined for a weight-loss indication could also be applied to an indication for the improvement of body-fat composition, using percent of body weight or percent of excess over ideal body weight or change in body mass index. Likewise, the guidance outlined for combination therapy for weight loss could also be applied for an improvement in body-fat composition.

7.1.3 Sustained Weight Reduction (i.e., weight-loss maintenance / prevention of regain)

In order to obtain an indication for sustained weight loss, the sponsor should demonstrate that after a period of prior weight loss, subsequent weight gain is significantly lower in subjects on drug than those on placebo, at the end of one year (i.e., weight rise above the new baseline established following documented weight loss is significantly lower on drug). The means by which weight loss had been achieved must be standardized within a given study (e.g., responders on prior drug therapy [monotherapy or combination therapy] or responders on a specified weight-loss program, such as Weight Watchers). Likewise, it may be possible to apply these criteria for an indication in individuals who have improved their body-fat composition.

7.1.4 Prevention of Weight Gain Associated with Other Effects (e.g., occurring with use of certain medications or during smoking cessation)

In order to obtain an indication for the prevention of weight gain, the sponsor should demonstrate that using either monotherapy or combination therapy, subjects on drug gain significantly less weight than those on placebo, at the end of one year.

Additional Endpoints for Consideration

Changes in parameters associated with risk factors, including measurements of central fat (e.g., waist-to-hip circumference, sagital diameter, or other direct measures of visceral fat mass) may be appropriate endpoints, depending on the population studied. Delay in the

onset of diabetes, osteoarthritis or other complication of obesity and or a positive benefit in the adjunctive treatment of obese patients with these comorbidities may also be a suitable endpoint in certain cases.

Measurement of obesity-associated cardiovascular risk factors (e.g., lipids, blood pressure and glucose tolerance) during drug administration is encouraged, as change associated with drug treatment may provide important considerations for prescribers/patients when assessing the expected benefits and risks of potential treatment options. Because the change in such factors are pertinent in making a benefit-to-risk decision for the drug, these findings (positive and negative) should be described in the drug's label.

In addition, patient reported outcome (PRO) endpoints should also be considered. These include endpoints of quality of life, patient satisfaction and patient preferences among others.

7.2 Duration of Trials

Pharmacological therapy must be viewed as part of a long-term strategy for weight management. As such, the duration of the clinical trials should be consistent to support the primary efficacy endpoint and intended use of the drug. Pharmacological therapy may be indicated for weight loss and or prevention of weight (re)gain. Depending on the desired indication /claim and overall profile of the drug, it could be possible for a sponsor to submit a marketing application for approval based on safety and efficacy following 12 months of exposure in at least 1500 subjects. If necessary, a sponsor's commitment to collect long-term safety data (e.g. 24 months), under actual clinical use conditions, may be required as part of a formal product surveillance program.

It is not intended that this Guidance encompass all possible evaluations for overweight and obesity. As the science evolves, opportunities not presented in this guidance may be identified and pursued. Accordingly, other proposed indications will be considered following submission of appropriate scientific rationale to the Division of Metabolic and

Endocrine Drug Products. As new drug entities with new modes of action are developed, modifications of the Guidance may become necessary.

This document is an informal communication under 21 CFR 10.90(b)(9) that represents the best judgment of the Division of Metabolic and Endocrine Drug Products at this time. This document does not necessarily represent the formal position of the Center for Drug Evaluation and Research or the Food and Drug Administration, and does not bind or otherwise obligate the Center or Agency to the views expressed.

Division of Metabolic and Endocrine Drug Products, Food and Drug Administration, 5600 Fishers Lane, HFD-510, Rockville, Maryland 20857-1706 (301) 827-6430.

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April 23, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane Rm 1061
Rockville MD 20852

Re: FDA Guidance for the Clinical Evaluation of Weight Control Drugs
Docket 2003D-0570

Dear Sir/Madam:

Nastech Pharmaceutical Company, Inc. respectfully submits the following comments on the FDA Guidance for the Clinical Evaluation of Weight Control Drugs:

Recommendation to change the focus of the Guidance to "Treatment of Obesity and Overweight":

We agree with the comments submitted by the American Obesity Association that the emphasis of the document should be shifted from "weight control" to "...the treatment of obesity and overweight." "Weight control" connotes cosmetic improvement; in fact the current Guidance mentions "self esteem" in the first sentence and "relatively healthy subjects" in Section 4. Therefore, as written, the Guidance seems to suggest that obesity is simply a "lifestyle" issue, and is somehow less medically important. Changing the focus of the document to "...the treatment of obesity and overweight" emphasizes the severe medical consequences now recognized to be caused by these conditions (for example, the March 9, 2004 announcement of a study from the HHS' Centers for Disease Control and Prevention showing obesity and overweight may overtake smoking as the leading preventable cause of death[1].

On safety evaluation of pharmaceuticals intended for the treatment of obesity and overweight:

We propose that the safety requirements in the Guidance be harmonized with the ICH E1A Guideline: Total exposure including short term exposure of 500-1500 patients; 300-600 patient exposure for 6 months; and an additional 100 patient exposure for 1 year. We respectfully suggest that this level of exposure is already conservative, as the E1A

[1] http://www.hhs.gov/news/press/2004pres/20040309.html

Guideline is subtitled "For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions" – and few would now argue that obesity and overweight are "non-life-threatening conditions." The Weight Control Guidance as currently written suggests a much larger safety database is required, with 1500 subjects completing 12 months and 200-500 completing 24 months. We suggest that such a large safety database should not be required for pharmaceuticals intended for an urgent and unmet medical need, unless signals of specific adverse events are identified during the development program.

We understand that following the unexpected cardiac valvular lesions encountered in patients taking the fen-phen combination, the Agency may have particular concern about drugs with a serotonin-associated mechanism of action. However, even for such drugs, data clearly indicate a signal for aortic regurgitation (adjusted odds ratio of 1.5 compared with controls and 4 cases of moderate-severe AR) in a randomly-selected sample of 313 patients on drug for 90-180 days and a statistically significant increase in prevalence of aortic regurgitation (adjusted odds ratio of 2.4 compared with controls ($p=0.0002$), and 5 cases of moderate-severe AR) in a randomly-selected sample of 415 patients on drug for 181-360 days (see Jollis et al. Fenfluramine and Phentermine and Cardiovascular Findings: Effect of Treatment Duration on Prevalence of Valve Abnormalities. Circulation 2000; 101:2071-2077). Therefore even in the case of drug-induced cardiac valvulopathy, the ICH E1A guidance of 300-600 patients on study for 6 months would be sufficient to generate a signal of an adverse event.

We also respectfully suggest that the safety requirements be tailored to the particular active moiety. For example, an endogenous peptide might be held to a different standard than a new molecular entity or a class of drugs known to cause specific adverse events. In other words, "one size fits all" may not be appropriate regarding the required safety database.

On efficacy evaluation of pharmaceuticals intended for the treatment of obesity and overweight:

Section 5.1 Population

The current Guidance requires that subjects with a body mass index (BMI) of 27 to 30 have at least one co-morbidity (hypertension, hyperlipidemia, glucose intolerance, cardiovascular disease, sleep apnea or other obesity-related condition). With the recognition that obesity is the second most common (and soon to be most common) cause of preventable death among Americans, and that many of the co-morbidities require years of obesity to appear and/or can be associated with irreversible conditions (osteoarthritis, for example) we respectfully request that the requirement of co-morbidities be removed. Furthermore, since the products are labeled for the treatment of patients who are overweight and or obese and since overweight is defined by all academic associations as a BMI from 25.0 to 29.9, there is no medical basis for setting the lower limit of treatment at a BMI of 27.0. By so doing, treatment is denied to millions of Americans with BMI values between 25 and 27.

Section 5.2: We have a concern regarding the requirement for a drug-free 6 week (or longer if weight loss continues) "run in" period. We believe that having a "run in" period, during which time weight loss does not count toward the efficacy of a pharmaceutical for the treatment of obesity and overweight, is neither a realistic measure of the overall efficacy of the combination of diet, exercise, lifestyle intervention and pharmaceutical, nor is it a standard that other classes of drugs are held to. There is, for example, no such requirement for pre-treatment diet and exercise regimens for cholesterol reduction before initiating statin treatment nor is there a requirement for intensive psychotherapy for depression before beginning SSRI administration. A fixed duration "run in" period does not provide useful data to practicing physicians who are confronted with the initiation of therapy in a given patient. Moreover, strictly speaking, a pharmaceutical for the treatment of obesity and overweight is not labeled for "post run in period" efficacy; therefore, the study design should not be so constrained.

We thank the Agency for the opportunity to comment on this Guidance, and look forward to a continuing dialog on the issue of pharmaceutical development for the treatment of obesity and overweight.

Respectfully submitted,

Gordon Brandt MD
Executive Vice President, Clinical Development and Medical Affairs
Nastech Pharmaceutical Company, Inc.

Pfizer Inc
Worldwide Regulatory Affairs & Quality Assurance
50 Pequot Avenue
New London, Connecticut 06320

Global Research & Development

April 26, 2004

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Draft Guidance on the Clinical Evaluation of Weight-Control Drugs
[Docket No. 2003D-0570, 68 *Federal Register*, 3588-3589, January 26, 2004]

Dear Sir or Madam,

Please make reference to the *Federal Register* notice of January 26, 2004 requesting review and comment of the early Draft Guidance on the Clinical Evaluation of Weight-Control Drugs [2003D-0570]. Thank you for the opportunity to comment. Attached are the Pfizer prepared comments on the Draft Guidance.

Given the interest in this topic, Pfizer suggests the Agency consider sponsoring a public workshop prior to releasing the next version of the guidance. We also invite direct dialogue with the Agency if you would consider the opportunity valuable.

Feel free to contact me if there is a need to clarify or expand on any of the points made in our comments.

Sincerely,

William R. Murphy, Ph.D.
Director, Pfizer Global Research and Development
Worldwide Regulatory Affairs

Pfizer Comments
Draft Guidance for the Clinical Evaluation of Weight-Control Drugs

General Comment:

Pfizer welcomes the opportunity to comment on the Food and Drug Administration's (FDA) Draft Guidance on the Clinical Evaluation of Weight-Control Drugs (1996). We applaud this effort to raise awareness and to solicit early comments from industry of key issues for the development of weight control drugs. We look forward to the issuance of the "formal" Draft Guidance as we share the FDA's commitment to the field of obesity and are looking forward to working with the Agency on addressing this major public health problem. As stated in the cover letter, Pfizer would welcome direct dialogue with the Agency or participation in a public workshop to facilitate final review and discussion of the guidance document before it is issued.

Our specific comments have been grouped under the following headings:

Include in the General Rationale:
- obesity is a chronic disease, which may require pharmacotherapy, in addition to diet, exercise and lifestyle modification
- 5% weight loss is associated with substantial health benefit
- reduction in body fat (weight) is associated with improvement in cardiovascular disease risk factors, sleep apnea, infertility, ...

Labeling Claims Achievable for Agents Reducing Body Fat (weight):
- Indication for weight loss
- Indication for prevention of weight regain (of recent weight loss)
- Indication for treatment of type 2 diabetes (and other obesity-related co-morbidities)
- Indication for prevention of type 2 diabetes (and other obesity-related co-morbidities)

Population:
For weight loss & prevention of weight regain indications:

- BMI > 30 for individuals without obesity related co-morbidities
- BMI > 25 for individuals with obesity-related co-morbidities (dyslipidemia, hypertension, type 2 diabetes, sleep apnea, infertility, osteoarthritis) or increased risk for development of these co-morbidities (e.g., positive family history)

Indication for treatment of type 2 diabetes:

- BMI>25 and diagnosis of type 2 diabetes per ADA criteria

Indication for prevention of type 2 diabetes:

- BMI>25 and diagnosis of "pre-diabetes" or diabetes per ADA criteria

Additional considerations:

- There should be another set of enrollment criteria based on total or central adiposity for all indications.
- Subjects who meet either the NCEP or WHO criteria for the metabolic syndrome should be eligible for inclusion regardless of their BMI. If these subjects are included, additional consideration should be given to independent labeling claims for this population.

Efficacy Criteria Definitions:

Indication for weight loss (needs to meet at least one of the three):

- Total weight loss from baseline ≥5% at 12 months and statistically significant difference between the treatment and placebo arms
- Placebo-adjusted weight loss ≥5% at 12 months
- Significantly greater proportion of individuals losing ≥5% and ≥10% of their initial body weight at 12 months

Indication for prevention of weight regain (of recent weight loss):

- Proportion of individuals who have maintained ≥80% of the initial body weight loss 12 months post-randomization is significantly greater in the treatment vs. the placebo arm.

Indication for treatment of type 2 diabetes (needs to meet one of the two):

- Reduction in HbA1c≥0.6% from randomization and statistically significant difference between the treatment and placebo arms at 12 months
- Placebo-adjusted difference in HbA1c≥0.6% at 12 months

Indication for prevention of type 2 diabetes:

- Significantly greater proportion of individuals with "pre-diabetes" progress into overt type 2 diabetes in the placebo vs. treatment arm

Run-in Period Prior to Randomization (reference Procedures):
Suggest eliminating this period from the design of the trials, rationale:

- Similar period is not used during trials for other chronic diseases (diabetes, hypertension, dyslipidemia)
- It is not standard clinical practice – patients who are candidates for pharmacotherapy for obesity have typically already tried diet + exercise multiple times
- The run-in period leads to selection bias, i.e., a subset of population otherwise eligible for treatment is arbitrarily excluded from the studies, thus reducing generalizability of the result
  - It can be used to select a population MORE likely to lose weight with intervention (if non-responders in the run-in are excluded), which would exaggerate total weight loss response above what might be seen in a more typical population.
  - If on the other hand subjects who respond during the run in are excluded, that eliminates from the trials subjects who would most likely experience a robust weight loss with all associated health benefits. Experience with other weight loss drugs (sibutramine) has demonstrated that the best predictor of long-term successful weight loss is the response during the first 4 weeks of therapy (4 pounds in 4 weeks).

From: Caccavella, Donna {PDR~Nutley} [donna.caccavella@ROCHE.COM]
Sent: Friday, April 23, 2004 1:09 PM
To: fdadockets@oc.fda.gov
Subject: Docket No. 2003D-0570, Response to FDA request for Input on 1996 Draft Guidance

Roche

April 23, 2004

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, Maryland 20852

RE: Docket No. 2003D-0570
Response to FDA request for Input on 1996 Draft Guidance

Reference is made to the Federal Register Notice dated January 26, 2004 (Volume 69, No. 16, pages 3588-3589) requesting comments on the previously published draft guidance entitled "Guidance for the Clinical Evaluation of Weight-Control Drugs". This draft guidance was originally issued September 24, 1996 and provided recommendations for the design and conduct of Phase 1-3 clinical studies aimed at demonstrating the efficacy and safety of Rx weight-loss medications. The Agency is now seeking to incorporate the latest scientific and medical information in the fields of obesity and drug development into an amended obesity guidance document.

In response to the above mentioned Federal Register Notice, Hoffmann La Roche, Inc. is herewith providing input/recommendations to the draft guidance for the clinical evaluation of weight loss drugs. Roche has carefully reviewed the 1996 draft guidance and is providing comments on the following specific issues which we believe should be considered for revision in the future guidance:

1. Indication Population

2. Selected Study Procedures including:
   - Lead-in period for Phase 2 and 3 studies
   - Duration of Phase 3 studies
   - Study population
   -

3. Obesity Related Risk Factors in the Product Label

4. Approval Criteria

2003D-0570

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Hoffmann-La Roche Inc. 340 Kingsland Street
Nutley, New Jersey 07110-1199

Background:
Roche is an ethical pharmaceutical company with extensive research interests in obesity and related metabolic disorders including diabetes. Roche has considerable experience in the field of obesity having been involved in research and development of potential weight control drugs for over 20 years. These research and development initiatives have resulted in the approval of XENICAL (orlistat), a pancreatic lipase inhibitor, approved for obesity management in the US as well as in over 120 other countries. Roche is the only pharmaceutical company to-date which has opened an IND for a weight loss drug candidate (orlistat) and taken that same drug candidate through both the IND development process and NDA approval process all within the Division of Metabolism and Endocrine Drug Products.

Based on current estimates, there have been over 19 million patient treatments with XENICAL to-date. Roche has conducted over 200 short-term and long-term controlled clinical trials (up to four years duration) assessing the safety and efficacy of potential anti-obesity agents including XENICAL. In addition to this experience in conducting clinical trials for potential weight loss agents, Roche has also conducted extensive focus groups and market research with both physicians whose clinical interests include weight management and treatment of obesity and with overweight and with obese patients. Moreover Roche has been engaged in continuous, ongoing dialogue with the major national and international medical associations, managed care organizations, and with national and international medical experts in the field of obesity and related medical disorders in order to better understand current developments in disease management. These activities have given Roche a broad understanding of obesity and its treatment from several points of view including current thinking in disease management, a good understanding of clinical practice in the treatment of obesity, of reimbursement and payers issues as well as an understanding of patients' needs.

It is against this unique background and knowledge base that Roche is providing the following input in response to the Agency's request for comments on the draft Guidance for the Clinical Evaluation of Weight Control Drugs. This response includes both our recommendations and the scientific/medical rationale for the recommendation addressed in this response.

1. Indication:
The current indication for weight control drugs is for the management of obesity, including weight loss and maintenance of weight loss when used in conjunction with a reduced-calorie diet. Drug candidates are approved for the treatment of obese patients with an initial body mass index of ≥30 kg/m^2 or ≥27 kg/m^2 in the presence of other risk factors (eg, hypertension, diabetes, dyslipidemia). Clinical trials for investigational weight loss drugs study these target populations in assessing the safety and efficacy of new drug candidates.

In light of the growing obesity epidemic in the US and understanding that, for some overweight patients with BMIs <27 kg/m^2, particularly those patients with one or more obesity related risk factors or with a strong family history of obesity or obesity related risk factors, medical and pharmacologic interventions should be considered to treat as well as possibly prevent or delay patients from progressing to a BMI of 27 or 30 kg/m^2. Such approaches for preventing disease progression and/or for treating the overweight population are consistent with the tenets of the NIH obesity research strategic plan, the recommendations of the American Medical Association, NAASO, and the NHLBI. We believe the future guidance should provide for the evaluation and labeling of potential weight loss agents in such an overweight patient population with BMIs >25 and <27kg/m2. Currently investigational weight loss agents do not study this lower BMI overweight population and physicians have no approved treatment options for such patients despite the acknowledged heath risks of excess body weight in this population as well.

2. Selected Study Procedures

2.a Lead-in Period for Phase 2 and 3 Studies

The lead-in period discussed in the current guidance suggests that patients should be entered into a weight reduction program including diet, behavior modification and exercise prior to being randomized into one of the treatment groups in the controlled clinical trial. After a 6 week lead-in period, if a patient does not lose weight or if weight loss has plateaued, only then should the patient be randomized into the study.

For long-term studies designed to assess the additive efficacy of a pharmacologic agent, this is not an appropriate element of clinical trial design. The purpose of large Phase 3 clinical trials is to determine whether or not a drug is sufficiently efficacious to be a reasonable adjunct to enhance weight loss. To require that the drug can only be studied and therefore only show efficacy when a person can no longer lose weight rather than to improve, extend or continue weight loss appears to be a standard of efficacy that is greater than those for related therapeutic areas. It is well accepted that the best predictor of long-term weight loss is the ability to lose weight during a short-term period. The lead-in period is an aggregate measure of a person's motivation including the ability to understand and maintain a diet and exercise program. As with all complex behavioral changes, there will be a broad spectrum of results. The goal of drug therapy for weight loss is to help patients across the spectrum increase their weight loss efforts and achieve a meaningful weight loss goal. Those who are potential good losers, losing a reasonable amount of weight during a short period of time, can have their ultimate weight loss increased by the drug under investigation while those who are potential poor losers can have the amount of weight they lose potentially increased with the use of the investigational drug treatment. Since the true measure of efficacy for a weight loss drug is the placebo subtracted weight loss difference, the total amount of weight a patient might loss is irrelevant in evaluating the real drug effect. When evaluating the true drug effect, it should make no difference if a person is actively losing weight, if an initial weight loss has plateaued or if a person is

unable to lose any weight at all. Based on Roche's obesity research data from studies conducted with orlistat, the weight loss effect was consistent regardless if patients were losing reasonable amounts of weight with diet and exercise or were resistant to these standard treatments in the lead-in period. In addition, the placebo subtracted weight loss effect of orlistat was similar regardless if the large Phase 3 studies had a placebo lead-in period prior to randomization to the study or if there was no lead-in period.

There is however one reasonable situation in a weight loss study for which a placebo lead-in period may have value and that is in studies with relatively small numbers of patients studied for short periods of time. Since it has been shown that patients who are initially able to lose weight will have greater ultimate weight loss than those who are poor initial losers, it is important to ensure that treatment groups are well balanced with respect to the number of potential good and poor losers. This could be an issue particularly in studies with relatively small numbers of patients studied for short periods of time. If the treatment groups are imbalanced and one group has a greater preponderance of good losers than another treatment group, the conclusion with regard to efficacy could be exaggerated. In larger studies, the randomization process has generally been shown to balance the groups well so that the conclusions with regard to size of the effect are not in doubt.

A final reason for not requiring a lead-in period is that this more closely represents what occurs once a drug is marketed. Patients turn to pharmacologic treatments for many reasons. Certainly some patients will try to lose weight by diet and exercise first, but many obese patients have been unsuccessful in the past and cannot or will not try diet and exercise again without the addition of something that may potentially make these efforts more successful. Studying the drug under actual use conditions will provide for a more realistic estimate of its' true effect and benefits when used in clinical practice.

2.b Duration of Phase 3 Studies

The current draft guidance suggests that prior to approval, drugs for the treatment for obesity need to be studied for 24 months for safety.

Obese patients in general are not inherently at any greater health risk than are patients with other metabolic or chronic conditions, therefore the requirement that the safety of an obesity treatment needs to be studied for two years of continuous treatment prior to approval is unjustified and not consistent with the requirements for many new chemical entities in related therapeutic areas. Unlike chronic treatments for diabetes or dyslipidemia, drugs for the treatment of obesity are frequently used for shorter periods of time. Based on Roche's obesity research program, controlled clinical studies for up to four years of continuous treatment with orlistat, for example, have shown that there were no additional related safety findings identified compared to those which had been identified

after the first year of treatment. Assuming that there are no signals from either pre-clinical evaluations or from shorter term clinical studies, safety in a large population of patients (500-1000) for one year should be sufficient prior to approval to establish a drug's safety profile in most cases. Depending on the mechanism of action of any particular drug, safety evaluations in some populations may have to be longer than a year, but there should be a definitive safety concern that needs to be monitored for longer than one year and in which one year safety evaluations would not suffice to define the safety profile of the drug candidate under clinical investigation. In addition, evaluation of chronic treatments with one year safety data prior to approval is consistent with the tenets of the ICH harmonization process and consistent with the recommendations of NAASO. Safety monitoring of the drug immediately after approval should provide for a far greater ability to detect very uncommon or even rare adverse findings which, as with all other therapeutic areas, generally cannot be detected during a clinical development program regardless of the size and duration.

2.c Study Population

Based on Roche's extensive experience in conducting multiple large Phase 3 clinical trials of one, two and fours years duration in overweight and obese patients, we recommend that Phase 3 study populations should include patients with hypertension, dyslipidemicia, impaired glucose tolerance, and/or metabolic syndrome. We do not recommend however including overweight and obese patients diagnosed and treated for type 2 diabetes in these Phase 3 weight loss studies. We recommend that this population be studied in separate weight loss studies. This recommendation is based on the difference response often observed in this patient population with respect to safety and efficacy, as well as for specific monitoring issues, e.g. a need to adjust diabetic medication to avoid hypoglycemia due to weight loss and improvement in glycemic control.

Roche also recommends that the guidance address the design and efficacy criteria necessary to assess the safety and efficacy of a drug candidate in the treatment of childhood/adolescent weight management. The current draft guidance is silent on recommendations for this important patient population.

3. Obesity Related Risk Factors in the Product Label

The current version of the draft guidance recommends assessing the effect of treatment on obesity-related risk factors in the Phase 3 trials and provides for the inclusion of this data in the label. Roche totally supports maintaining these recommendations in the new guidance. Our extensive interactions and experience with physicians who use pharmacologic intervention in the treatment of their overweight and obese patients, confirms that the effects of treatment on obesity-related risk factors are of great importance in prescriber's benefit/risk assessment for treatment. Therefore we feel it is necessary to not only generate these data in a controlled clinical trial setting but also to include the data in the approved label so that the data are readily accessible to physicians. In addition, it is well

accepted that excess body weight is one of the major underlying causes for the development of type 2 diabetes. Currently approved treatments for type 2 diabetes use the change in HbA1c as the prime efficacy evaluation and the mechanism responsible for the change, while scientifically interesting, is not itself being assessed. Similarly, if a drug produces sufficiently more weight loss than placebo and produces a meaningfully greater decrease in HbA1c, than this should be an indicated use for the drug. The mechanism of action, being weight loss, should not be considered less meaningful than drugs with either unknown mechanisms or other cellular based mechanism that merely lower glucose levels but don't change the key cause of type 2 diabetes, excess body weight.

4. Approval Criteria

The current draft guidance states that there are two key methods for measuring the weight loss efficacy of a compound. The first is to determine if the absolute mean placebo subtracted weight loss difference is at least 5% of the patients' baseline body weight. The second method, also known as the categorical analysis, is to determine if the percentage of patients who reach and maintain a loss of at least 5% of their baseline body weight at the end of 1 year of treatment is significantly greater in patients on drug than on placebo. Roche supports maintaining these criteria but recommends some additional considerations for the categorical analysis approval criteria.

It should be noted that since all patients should also be receiving other supportive interventions such as diet, exercise and possibly behavior modification, both these weight loss criteria are more rigorous than if no adjunctive treatment were be used at all. It is important to show both that background treatment with diet, exercise and placebo did in fact produce a weight loss and that active drug in addition to diet and exercise produced an even greater weight loss.

As presented in detail during the 1997 Advisory committee meeting discussing the approval criteria, for weight control drugs, a weight loss of 5% is considered the level at which clinical benefits are observed and which is consequently one of the most import aims of pharmacologic intervention. This 5% criteria is also supported by several medical associations including NAASO, AMA, ADA and AOA.

However, for some patient populations other considerations must be given when assessing efficacy. Under certain circumstances such as in children and adolescent who are still growing, preventing additional weight gain rather than an actual weight loss is also reasonable criterion for efficacy. It has also been established in clinical studies such as those performed with orlistat in obese and overweight patients with type 2 diabetes, even less weight loss was associated with clinical benefits and improvements in obesity-related risk factors.

To insure that the incremental effect of drug treatment is confirmed, the second approval criterion could be further defined to specify the required difference between treatment groups in the percentage of patients achieving a 5% weight loss. This would prevent a drug with a too-small difference in response between treatment groups from being considered for approval. For example it would be reasonable to say that the absolute difference between the percentage of patients losing at least 5% of their baseline body weight on drug compared to placebo should be at least 15-20% (as well as being statistically significant). This would mean if 30% of placebo patients lost at least 5% of their bodyweight, then 45-50% of the drug treated patients would need to lose at least 5% of their body weight. These are sufficiently rigorous criteria that, if achieved, would confirm that a drug is very efficacious.

Based on our experience in obesity drug development as well as on numerous and ongoing discussions with medical experts, physicians and patients, Roche believes that the current efficacy guidelines are adequate to define a clinically meaningful weight loss and should be maintained in the revised future guidance. We do believe that, for approval based on the categorical analysis criteria, some consideration could be given in the revised guidance to further define the degree of difference between treatment groups in the percentage of patients achieving a 5% weight loss at the end of one year.

In summary, Roche remains committed to the study of obesity and its management as well as other related therapeutic areas and welcomes the opportunity to comment on this importance guidance. With regard to this response, Roche will be happy to provide additional information on any of the recommendations included in this communication.

Sincerely,

HOFFMANN-LA ROCHE, INC.

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CD/dc

HLR No. 2004-1028

Michael Garvin, Pharm.D.
Director
Scientific and Regulatory Affairs

PhRMA

April 23, 2004

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Request for Comments on a Draft Guidance on the Clinical Evaluation of Weight-Control Drugs [Docket No. 2003D-0570, 69 *Federal Register*, 3589, January 26, 2004]

Dear Madam/Sir:

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading pharmaceutical research and biotechnology companies, which are devoted to inventing medicines that allow patients to live longer, healthier, and more productive lives. PhRMA members invested an estimated $33.2 billion in 2003 in discovering and developing medicines. PhRMA companies are leading the way in the search for new cures.

PhRMA welcomes the opportunity to provide the attached comments on a Draft Guidance on the Clinical Evaluation of Weight-Control Drugs and would appreciate your careful consideration of these comments as you work to revise this document.

Please contact me if there are any questions regarding these comments.

Sincerely,

Michael Garvin

Michael Garvin, Pharm.D.

Pharmaceutical Research and Manufacturers of America
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2003D-0570

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Comment on Guidance for the Clinical Evaluation of Weight-Control Drugs (9-24-96)

General Comments:

In the past seven and one half years since the publication of the Guidance for the Clinical Evaluation of Weight-Control Drugs, it has become increasingly clear that obesity is a serious and growing medical problem in the US and throughout the world. Obesity as a disease is causally linked to insulin resistance, Type 2 Diabetes Mellitus (DM), hypertension (HTN), cardiovascular disease, cancer, arthritis, respiratory and sleep disorders. The initial treatment of obesity is based on caloric restriction and the maintenance or increase in physical activity to induce weight (fat) loss. Unfortunately this is not effective in the vast majority of people. Pharmacological therapy plays a crucial role when diet and exercise fail. Treatment of the underlying obesity can improve the comorbidities, as seen with Type 2 DM, dyslipidemia, and hypertension.

The updated Guidance for the Clinical Evaluation of Weight-Control Drugs should more closely reflect the causal link between obesity and the diseases mentioned above (insulin resistance, Type 2 Diabetes Mellitus (DM), hypertension (HTN), cardiovascular disease, cancer, arthritis, respiratory and sleep disorders). The reference to obese subjects as 'relatively healthy' sends the wrong message and the language throughout the Guidance should reflect the significance of obesity as a disease.

The updated Guidance should parallel the Guidance for other chronic conditions (Type 2 DM, dyslipidemia, and hypertension). There should be appropriate demonstration of safety and efficacy that warrants the appropriate use of these agents.

As indicated in FDA's recently issued paper on Innovation Stagnation (US Department of Health and Human Services, March 2004), the FDA is uniquely positioned to help identify the challenges of developing safe and effective therapeutic agents. The obesity guidance revision process will be greatly enhanced by broad consultation with experts in the field, and we therefore encourage the FDA to take full benefit of the larger scientific and medical community on developing solutions in the field of obesity research.

Specific Comments

1. Introduction:
    a. The Introduction should identify the significant health risk of excess weight (adipose tissue) and move away from implications of obesity as a lifestyle problem or merely a problem with 'self-esteem'.
    b. The use of the terminology "weight-control" should be replaced with the "prevention and treatment of obesity".
    c. It would be important to clarify the statement "only those aspects of the trials that are specific to weight-control drugs". It would be important to identify appropriate assessments for safety and efficacy (both weight loss requirements and associated measurements of obesity related disorders) for the evaluation of drugs for the prevention and treatment of obesity.
    d. Reference to "healthy obese" or "otherwise healthy" should be eliminated and replaced with "obesity uncomplicated by associated co-morbid disease".

2. General Rationale:
    a. This crucial section should be expanded to amplify the important role of obesity in multiple costly diseases including Type 2 DM, HTN, cardiovascular disease, cancer, arthritis, respiratory and sleep disorders.
    b. It would be important to identify the recognized benefit of treating obesity with respect to Type 2 DM, HTN, cardiovascular disease, cancer, arthritis, respiratory and sleep disorders.
    c. The discussion of the natural history of weight changes (loss followed by regain) is important and should be amplified. It is clear that short-term therapy does not lead to lasting benefit. The need to address excess weight as a chronic disorder requiring chronic intervention is important in order to realize the full benefit of weight loss.
    d. As suggested in the Guidance, unique mechanisms of action of agents in the future may allow a successful maintenance of weight lost. This concept is an important one to include in consideration of "long term safety and efficacy".
    e. This Guidance should be consistent with other guidelines for chronic use therapies in the metabolic area (DM, HTN, dyslipidemia) regarding the assessment of safety and efficacy.
    f. The current guidance document states that "weight is frequently (usually) regained promptly after it has been lost if the weight loss was induced by weight-control drugs and the drugs have been discontinued". This statement should be removed since it is common to have a rebound effect when either pharmacological intervention or non-pharmacological intervention is terminated (Clinical Guidelines of the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, The Evidence Report, NIH September 1998). Weight maintenance interventions should be considered a chronic intervention with potentially life-long therapies in the same context as treatment of other metabolic and CV risk factors & diseases (dyslipidemia, hypertension).

3. Early Clinical Trials
   a. Consider defining this as Phase 1.
   b. We recommend adding the early study of pediatric, adolescents and young adults, as these groups are significantly affected.

4. Dose Range Finding
   a. Consider defining this as Phase 2.
   b. We recommend deleting the first sentence sine it implies that excess weight is not a serious concern ("relatively healthy" subjects). The reference to the "drug dose recommended not be excessive" is addressed in the second sentence.
   c. The choice of doses will depend on the proposed mechanism of action. The guidance should therefore not set a lower limit on the number of doses required for study. It would be ideal to allow this flexibility while perhaps providing the usual number of doses (i.e. "at least 3 doses...").
   d. The guidance should also address the possibility of different dose regimens, such as continuous or intermittent treatment for weight loss, weight maintenance and use in combination with other obesity treatments.
   e. The subjects in these Phase 2 / Dose range studies should be similar to those that will be studied in the Phase 3 / Trials to Establish Efficacy.
   f. The current Guidance identifies individuals who are overweight (BMI>27) with comorbidities or who are obese (BMI>30) as relevant subjects for study. This unnecessarily limits the addressable population. The description of relevant subjects for inclusion should be changed to incorporate the definition of excess weight from the WHO and NHLBI recommendations in conjunction with the current guidelines.

   Recommendations:
   a. BMI-25 to 30 (over weight) with an associated comorbidity (insulin resistance, Type 2 DM, HTN, cardiovascular disease, cancer, arthritis, respiratory and sleep disorders)

   or

   b. BMI ≥ 30 with or without an associated comorbidity

5. Trials to Establish Efficacy

Consider defining this as Phase 3.

5.1 Population

a. The current guidance states, "Subjects in long term trials should be moderately to markedly obese with BMI at least 30 for otherwise healthy individuals, and BMI at least 27 for those with comorbidities". These restrictions are inconsistent with the understanding that risk of excess weight begins at a BMI below 27. As in section 4 (Dose Range Finding), the WHO and NHLBI recommendations consider subjects with a BMI between 25 and 30 as being overweight. Expanding the

addressable population would enable effective study of weight-control drugs in the relevant population.

b. The Guidance should recognize and define the Metabolic Syndrome (The National Cholesterol Education Program Adult Treatment Panel III report defined metabolic syndrome as the presence of any 3 of the following 5 risk factors: abdominal obesity, elevated triglycerides, decreased HDL, increased blood pressure, or impaired fasting glucose). The Guidance should consider the inclusion of subjects who meet the criteria for the Metabolic Syndrome.
c. It is important to identify subjects with excess adiposity. Although BMI is an excellent marker, it will be important to look beyond BMI. It would be useful to identify the utility of waist circumference, W/H ratio, skin fold assessment, BIA, and DEXA as potential measurements to enhance specificity for excess adiposity.

5.2 Procedures

The intention of this section is critical for the evaluation of efficacy and safety of weight control drugs. It is imperative to efficiently and effectively assess the activity of a drug candidate to impact body weight in an unbiased way.

a. The description of the subject selection with a pre-drug treatment weight loss phase is described within this section. This is perhaps only relevant for otherwise qualified subjects who have never attempted weight loss. In this case it is not clear if the subject could lose weight without the use of a drug. But, a vast majority of subjects have had multiple attempts to reduce their weight and have not been successful. The subject selection process as described is not feasible, and should be modified to allow subjects who have attempted and failed to lose weight historically to enroll without the further hurdle of weight loss criteria during a lead-in.
b. The utility of a hypocaloric lead-in phase within a study is perhaps more relevant for short-term studies (up to 6 months). Since data for long term (1 year) trials are required for efficacy, and changes of weight after 1 year are not affected by the lead-in weight loss phase, it should be feasible to remove this requirement.
c. In addition to the biomarkers currently listed in the guidance document we suggest that the following additional CV biomarkers for assessment be considered where applicable for agents with potential to demonstrate benefit: left ventricular mass, inflammatory markers (e.g. C-reactive protein) and clotting factors (e.g. PAI-1 and fibrinogen).
d. The efficacy endpoint evaluation should reflect the relevance of modest weight loss and the maintenance of that loss to achieve improvements in obesity associated disorders.

Indication for weight loss (needs to meet at least one of the three):

- Total weight loss from baseline ≥5% at 12 months and statistically significant difference between the treatment and placebo arms
- Placebo-adjusted weight loss ≥5% at 12 months

- Significantly greater proportion of individuals losing ≥5% and ≥10% of their initial body weight at 12 months

Indication for weight maintenance

The draft guidance suggests that maintenance of weight loss may be the principal benefit of anti-obesity therapy. Further clarification on the design of studies to demonstrate weight maintenance should be detailed in the future guidance. Three treatment paradigms could be proposed to assess weight maintenance: (1) weight maintenance after drug-induced weight loss, (2) weight maintenance after diet-induced weight loss (e.g. 6 weeks of a very low calorie diet) or (3) prevention of weight gain associated with use of certain medications (e.g., sulfonylurea, anti-psychotics, anti-epileptics, corticosteroids, etc.) or therapies (e.g., smoking cessation). In the first two paradigms, it should be possible to demonstrate the efficacy of drug-treatment to reduce body weight regain (or further decrease body weight) in studies of one year duration or less. Sponsors should assess the between-group difference in proportion of patients who maintain a clinically meaningful degree of weight loss (e.g., 5% of baseline body weight). For the third paradigm, it should be possible to demonstrate efficacy by establishing a statistical difference in weight gain between the drug- and placebo-treated groups in studies lasting one year or less.

5.3 Duration of Trials

a. Efficacy: A one year trial for efficacy is consistent with guidelines for other drugs used to treat metabolic disorders. Further, studies have shown maximal effect of weight loss drugs are evident within 6-12 months.
b. Safety: As it is adequate for a 1 year exposure for drugs used to treat Type 2 DM, HTN, and dyslipidemia, it is not clear why agents used to treat obesity should be required to be studied for 2 years. Given the desire to ensure safety in a drug that would be used chronically and make this consistent with the other Guidances, the duration of study should be 1 year for approval with a need to develop longer term (2 year) safety data if approved.

Additional Considerations

Accelerated approval/Fast track requirements:
Obesity is now recognized in the US as a serious and life-threatening disease. The Guidance should consider weight loss drugs as eligible for accelerated approval and Fast Track designation.

Abuse Liability Assessment:
Many anti-obesity agents are centrally-acting anorectics which may require assessment of abuse liability potential (21CFR 314.50(d)(5)(vii)). A distinction should be made in the future guidance between misuse (e.g. weight loss in non-obese subjects) and abuse (e.g., unintended use of product). The absence of clear guidance for the assessment of abuse liability may hamper progress in the development of novel therapeutic agents. The FDA could clarify this by issuing the pending guidance on Assessment of Abuse Potential of Drugs or provide specific direction to Sponsors on the preclinical/clinical studies required to assess abuse liability.

Metabolic Syndrome
Given the potential benefit for improvement in the Metabolic Syndrome with the treatment of obesity, and the clear link to increased cardiovascular morbidity and mortality, the Guidance should delineate a path toward an indication for the Metabolic Syndrome.

From: Nearing, Toni-Marie [PRDUS] [TNearing@prdus.jnj.com]
Sent: Monday, April 26, 2004 4:23 PM
To: 'FDADockets@oc.fda.gov'
Subject: Company Comments for Docket No. 2003D-0570

Follow Up Flag: Follow up
Flag Status: Flagged

Good afternoon. Attached below is a copy of the cover letter and the comments and recommendations from the pharmaceutical business and research organization of the Johnson & Johnson family of companies. These comments are in response to the FR notice on the FDA's Draft Guidance of the Clinical Evaluation of Weight- Control Drugs. A hard copy of these documents was Federal Expressed to the Docket Management Branch (HFA-305) this past Friday, April 23rd.
If you have any questions regarding this submission, please contact me. Thank you for the opportunity to comment on such an important topic.

Regards - tmarie
Toni Marie Nearing-Crowley
Director, Regulatory Affairs
FDA Liaison Office, J&JPRD
(301) 881-6974 extension 229

Johnson & Johnson
PHARMACEUTICAL RESEARCH
& DEVELOPMENT, L.L.C.

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1051
Rockville, MD 20852

FDA Docket No. 2003D-0570
Request for Comments on a Draft Guidance of the Clinical Evaluation of Weight-Control Drugs

Dear Sir/Madam:

As leaders in the discovery, development, manufacturing and marketing of prescription medicines, the pharmaceutical business and research organizations in the Johnson & Johnson family of companies are committed to improving health and well being through innovative products and services. I am sending these comments on their behalf.

We fully support the FDA's interest in incorporating the latest scientific advances in the field of obesity and drug development into an amended obesity guidance document. The current epidemic of obesity in the U.S. needs to be addressed and it is encouraging that Tommy Thompson, Secretary of Health and Human Services (HHS) has kicked off a major initiative on obesity to convert opinion that obesity is a medical concern not a life style issue. Acting Commissioner Lester Crawford has stated that obesity-related deaths in the U.S. have increased to 400,000 per year, up from 300,000 two years ago. He predicted the number will exceed 500,000 deaths per year by the end of this decade and at that point will likely overtake tobacco as the leading cause of death in the U.S.

Although not a complete and total answer, pharmacological intervention has an integral role along side other treatments (e.g. bariatric surgery) and lifestyle modifications in curbing the obesity epidemic and reducing the incidence of associated diseases such as diabetes and hypertension that are well recognized as major contributors to the onset of cardiovascular morbidity and premature cardiovascular mortality. The treatment of obesity includes induction of weight loss, maintenance of weight loss and prevention of weight gain. As such, it needs to be recognized that available therapies may provide valuable benefit to one phase of the treatment paradigm.

The guidance should address the recent emergent environment associated with obesity such as metabolic syndrome and childhood obesity. With newer and novel therapeutic approaches to treat obesity and the associated morbidity and mortality, we encourage

FDA to take into account clinically relevant improvements in co-morbid disease bio-markers (HbA_{1c}, blood pressure, lipids etc.) whilst determining the benefit-risk of a new agent. We further encourage the Agency to utilize all resources at their disposal to expedite delivery of new therapeutic options to obese patients.

We believe the obesity guidance revision process will be greatly enhanced by broad consultation with experts in the field and therefore encourage the FDA to take full benefit of the larger scientific and medical community on developing solutions in the field of obesity research. As indicated in FDA's recently issued paper on Innovation Stagnation (US Department of Health and Human Services, March 2004), the FDA is uniquely positioned to help identify the challenges of development with the goal of promoting efficient development of safe and effective new medical treatments.

In closing, we appreciate the opportunity to comment on this very important draft guideline. We look forward to working alongside the FDA with the goal of promoting efficient development of safe and effective new medical treatments for obesity.

Sincerely,

Jacqueline A. Coelln, R.Ph.
Director
Regulatory Affairs

GENERAL COMMENTS

Overall, this is a very important draft guideline that will have a significant impact on development of drugs for the treatment of obesity, a chronic metabolic disease. However, at this point, it requires major revisions and we fully support the current efforts to update this guidance. The document dates from 1996, so it could not be expected to address the recent emergent environment associated with obesity; metabolic syndrome, childhood obesity, or the fact that the epidemic of obesity continues to progress largely unchecked. Although not a complete and total answer, pharmacological intervention has an integral role along side other treatments (e.g. bariatric surgery) and lifestyle modifications in curbing the obesity epidemic and reducing the incidence of associated diseases such as diabetes and hypertension that are well recognized as major contributors to the onset of cardiovascular morbidity and premature cardiovascular mortality.

Control of obesity can result in a variety of health benefits and outcomes. It is well documented that even modest weight loss has been associated with clinically significant improvements in hypertension, lipid abnormalities, ischemic heart disease and reduced risk of developing type 2 diabetes (Clinical Guidelines of the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, The Evidence Report, NIH September 1998). These documented patient benefits need to be communicated to prescribers and patients, potentially forming the basis for label claims. With newer and novel therapeutic approaches to treat obesity and the associated morbidity and mortality, we encourage FDA to take into account these clinically significant improvements whilst determining the benefit-risk of a new agent. We further encourage the Agency to utilize all resources at their disposal to expedite delivery of new therapeutic options to obese patients.

It should be recognized that an obesity agent could provide a valuable benefit for only one stage of the treatment phases / potential indication statements for obesity, for example: induction of weight loss, maintenance of weight loss, prevention of weight gain, reduction in morbidity and/or mortality, e.g., cardiovascular disease, type 2 diabetes, malignancies, respiratory disorders, etc. Therefore FDA guidance should delineate recommended clinical development programs (e.g. trial designs, clinical endpoints (single endpoints and/or possible composite outcome measures), duration of treatment, etc) for each phase.

We believe the obesity guidance revision process will be greatly enhanced by broad consultation with experts in the field and therefore encourage the FDA to take full benefit of the larger scientific and medical community on developing solutions in the field of obesity research. As indicated in FDA's recently issued paper on Innovation Stagnation (US Department of Health and Human Services, March 2004), the FDA is uniquely positioned to help identify the challenges of development with the goal of promoting efficient development of safe and effective new medical treatments.

Below is the Johnson & Johnson family of companies comments directed at the wording in the 1996 draft obesity guidance; comments are provided for each section of the draft guidance.

1 INTRODUCTION

We suggest replacing the terminology "self-esteem" with "patient reported outcomes", as "self-esteem" represents a very limited perspective and tends to understate the serious impact of the obese condition and the compelling need for treatment. "Patient reported outcomes" provide the broader understanding of the patient's perception of their general functioning and well being including domains such as health status, symptoms, psychological and social functioning. This type of evaluation may be valuable to include in the product labeling, therefore, we recommend that the guidance address instruments (tools) that can be used to measure and report patient reported outcomes.

In addition, we recommend that reducing or maintaining body weight, or preventing body weight gain be added to reducing body fat as a demonstration of the safety and efficacy of obesity treatments.

We suggest replacing the terminology "weight-control drugs" with the description "drugs for the treatment of obesity".

In addition, the WHO definition of the term obesity should be described in the introduction or general rationale sections:

- BMI $\geq$25kg/m^2 for overweight (Pre-obese: BMI $\geq$ 25-29.9 kg/m^2)
- BMI >30kg/m^2 for obesity:
  - Class I obese: BMI 30-34.9kg/m^2 (Moderate)
  - Class II obese: BMI 35-39.9kg/m^2 (Severe)
  - Class III obese: BMI 40kg/m^2 (Morbid)

Reference to "healthy obese" or "otherwise healthy" should be eliminated and replaced with "obesity uncomplicated by associated co-morbid disease".

We generally agree with the BMI definitions for the population to be treated as outlined in the current guidance. However, given the growing body of scientific evidence that overweight patients are at increased risk for co-morbid diseases, including the observation of a J-Shaped relationship between body-mass index and overall mortality from the prospective Nurses' Health Study that examined the health consequences of being mildly to moderately overweight in association with mortality, the FDA may wish to consider the relevance of modifying a portion of the criteria to include patients with a BMI $\geq$25kg m^2 with co-morbidities.

2 GENERAL RATIONALE

We strongly urge the FDA to discuss in this guidance the relationship of obesity with type 2 diabetes mellitus. The increasing prevalence of obesity is a major public health concern associated with increased incidence of hypertension (HTN), dyslipidemia and type 2 diabetes mellitus. Further, as childhood obesity is increasing there is evidence that the onset of type 2 diabetes is no longer limited to those in their forth or fifth decade of life. Diabetes is associated with significant morbidity and mortality due to microvascular (retinopathy, nephropathy, and neuropathy and neuropathic complications) and macrovascular (cerebrovascular and cardiovascular diseases) complications. The association of obesity with diabetes is well established, and obesity is now accepted as a major risk factor for the development of type 2 diabetes; approximately 80% of patients with type 2 diabetes are overweight. As body weight increases, the risk of type 2 diabetes increases linearly. From the Diabetes Prevention Program (DPP), intensive lifestyle intervention led to weight loss and associated with that weight loss was a delay in the onset of diabetes by 58%.

In addition to the co-morbidities that result from excess weight, there are also decreases in patient perceptions of functioning and well being and changes in other patient-reported outcomes associated with obesity (e.g. symptoms). (Patrick, et al. Performance of two self-report measures for evaluating obesity and weight loss. Obesity Res 2004;12:48-57).

Furthermore, obesity imposes a significant economic burden on society. Annual medical expenditures of obese adults under 65 were estimated to be 36% higher than those of normal weight (R. Sturm "The Effects of Obesity, Smoking, and Drinking on Medical Problems and Costs", Health Affairs March/April 2002:245-253.) In 2002, $92.6 billion of annual medical spending was attributable to being overweight or obese (E. A. Finkelstein et. al. "National Medical Spending Attributable To Overweight and Obesity: How Much, And Who's Paying?" Health Affairs, May 2003:219-226.) These estimates of the full societal economic effect are underestimated, as they do not include non-direct medical costs, such as losses in worker productivity.

Currently approved pharmacological therapies for the management of obesity are indicated for both weight loss and weight maintenance. It should be recognized that an obesity agent could provide a valuable benefit for only one phase of the treatment paradigm, and therefore specific (e.g.; trial duration, endpoint evaluation, etc.) guidance for each phase should be provided in the appropriate sections of this document. In addition, a separate discussion of the development of pharmaceuticals for the prevention of obesity and early treatment intervention, including childhood interventions should be included.

The current guidance document states that "weight is frequently (usually) regained promptly after it has been lost if the weight loss was induced by weight-control drugs and the drugs have been discontinued". This statement should be removed since it is common to have a rebound effect when either pharmacological intervention or non-pharmacological intervention is terminated (Clinical Guidelines of the Identification,

Evaluation, and Treatment of Overweight and Obesity in Adults, The Evidence Report, NIH September 1998). Weight maintenance interventions should be considered a chronic intervention with potentially life-long therapies in the same context as treatment of other metabolic and CV risk factors & diseases (dyslipidemia, hypertension). Thus suggesting that a new "set point" will be developed after the cessation of drug administration is not valid.

3 EARLY CLINICAL TRIALS

Consistent with the current PK guidelines, we support the inclusion of both healthy volunteers and obese patients without significant co-morbidity for evaluation in the early phase clinical trials. And while the statements regarding the inclusion of a minority and gender mix is valid, this comment is more applicable to larger Phase 2b and 3 studies for which useful clinical data may be obtained. In addition, the high prevalence of metabolic syndrome and co-morbidities in the obese population implies that concomitant use of antihypertensives, lipid lowering and hypoglycemic agents, among others, will occur. As such, for those concomitant drugs that may have a narrow therapeutic window and may have a potential for pharmacokinetic or pharmacodynamic interaction with the drug agent under development, consideration should be given to conducting early drug-drug interaction trials for co-morbid treatments.

The mechanism of action is an important consideration for the development of any new agent. However, it is a complex undertaking, which may not be feasible to fully elucidate in a short time frame, and therefore is frequently not practical to define in early clinical studies. It should be investigated thoroughly, and in parallel with the whole development program. In early mechanism probe trials, hypothesis generating studies for the mechanism(s) of action may be useful, such as investigating a dose dependent change in a biomarker that suggests a certain mechanism of action (e.g. reduction of food intake for appetite suppressing drugs, fecal fat content or postprandial triglyceride absorption for fat absorption inhibiting agents). Subsequently, if proven to correlate with and be reasonably interpreted as causative of the weight loss, these biomarkers can be used as surrogate markers of weight loss and be of clinical utility in early proof of clinical concept trials where study duration is too short to demonstrate weight loss.

If there is theoretical rationale for a differentiated response (exaggerated or diminished) to a drug in a certain cohort of patients, the study design should aim to identify and characterize this cohort (e.g. by using a pharmacogenomic approach).

4 DOSE RANGE FINDING

We agree with the general description of the design considerations as stated in the 1996 draft guidance for dose-range finding clinical trials. We do however recommend:

- That the identification of a lower dose needs to be " a clinically relevant drug effect " rather than the current wording of " an optimal drug effect"

- That "similar instruction in diet, exercise and behavioral interventions" be replaced with, "standardized instruction in diet, exercise and behavioral interventions" to be given across sites within a study to eliminate the potential influence of site to site variability of ancillary interventions on weight loss response.

- Those patients with certain co-morbid risk factors (e.g. hypertension & dyslipidemia), which do not historically interfere with weight loss response, be included in phase 2b trials.

- Consideration be given to dose ranging in specific obese populations if these are to be the focus of a phase 3 development program (e.g. severe or morbid obese, obese subjects with type 2 diabetes).

- The population under study in dose-finding should be diagnosed as obese by accepted diagnostic convention and be broadly similar in demographic composition to the proposed phase 3 population. This population should therefore be considered similar demographically, ethnically and in terms of predicted drug response, to a representative US obese population.

The guidance should also address the following scenarios: the possibility of different dose regimens, such as continuous or intermittent treatment; dose ranging for weight loss, dose ranging for weight maintenance and dose ranging for use in combination with other weight control agents.

5 TRIALS TO ESTABLISH EFFICACY

As indicated in FDA's recently issued paper on Innovation (US Department of Health and Human Services, March 2004), much more attention and creativity need to be applied to disease-specific trial design and endpoints intended to evaluate the effects of medical products.

As discussed earlier, weight loss, weight maintenance, as well as obesity prevention should be described, along with the general and specific parameters for consideration during drug development programs (e.g.; trial duration, dose selection, efficacy assessment tools (parameters), efficacy endpoints).

As also mentioned previously diet, exercise and behavioral interventions should be standardized within a study to eliminate the potential influence of variability of ancillary interventions on weight loss response. It is suggested that caloric content of the background hypocaloric diet should be assessed individually according to the subject's calculated daily energy requirements. Because of the influence of body weight on this, these requirements should be recalculated periodically during long-term studies. Lower doses or a eucaloric diet should be considered when assessing long term weight maintenance following weight reduction.

We are encouraged by the FDA collaboration with NIH in addressing the need to improve the efficiency and effectiveness of the clinical trial process, including trial design, endpoints and analyses through its *Roadmap* initiative.

5.1 POPULATION

As provided for earlier in these comments, the WHO definition of the term obesity should be described as the guidance for patient populations to be studied:

- BMI $\geq$25kg/m^2 for overweight (Pre-obese: BMI $\geq$ 25-29.9 kg/m^2)
- BMI >30kg/m^2 for obesity:
  - Class I obese: BMI 30-34.9kg/m^2 (Moderate)
  - Class II obese: BMI 35-39.9kg/m^2 (Severe)
  - Class III obese: BMI 40kg/m^2 (Morbid)

Including consideration for modifying a portion of the criteria to include patients with a BMI $\geq$25kg/m^2 with co-morbidities instead of $\geq$27kg/m^2.

The sentence "It is often preferable to identify obesity by methods that measure body fat and its distribution", suggests that this type of measure should replace weight or BMI as a primary endpoint measure. We agree that the measure of body fat and its distribution is an import factor and suggest the wording be modified to reflect fat assessment as an additive measure, rather than an a replacement measure to weight and BMI. Associated with this comment, a more detailed description regarding the identification of an appropriately powered subset of subjects with visceral obesity needs to be given. For instance, visceral obesity can be indirectly assessed through anthropometric assessments such as waist circumference or directly via more intensive imaging modalities such as CT scanning, DEXA or MRI. Often, assessment of a representative proportion of male subjects will allow a better opportunity for assessment of visceral fat in subject population with a greater degree of visceral obesity.

We question the value of including the demographics of "socioeconomic status and education level" of a subject as these factors do not have a causal relationship to the efficacy of an agent and should therefore be deleted.

5.1 PROCEDURES- SUBJECT SELECTION

We strongly disagree with the requirement for a 6-week non-pharmacological weight loss run-in period prior to study inclusion. As discussed in the General Rationale section of this document non-pharmacological weight loss while often successful in initial weight reduction is also commonly associated with weight re-gain over time. It is highly unusual for an obese subject to enter a study of an investigational agent unless they have

previously attempted other weight loss modalities, and these previous failed attempts can be ascertained through medical history.

From a study design perspective run in periods have revealed a minority of subjects that achieve a clinically relevant weight loss that would preclude intervention. This makes subjecting all subjects to this regimen of doubtful clinical benefit and adds unnecessary time and cost to study conduct. From the medical perspective are the unusual baseline conditions such run-in periods present. Subjects are usually placed on caloric restriction during this period resulting in significant metabolic changes. This includes lipid (particularly triglyceride) and glucose changes that make tne interpretation of the baseline value (i.e. at the time of drug intervention) extremely difficult.

In addition this requirement presents an inconsistency with guidance for other chronic metabolic conditions (lipid-lowering, anti-hypertensive or anti-diabetic agents). We suggest the Agency consider a short (2-4 week) placebo weight maintenance run-in period to establish drug compliance and evaluate an accurate baseline metabolic status in a eucaloric setting.

5.1 PROCEDURES- ENDPOINT EVALUTION

We generally agree with the requirements for demonstration of a weight-loss or maintenance of at least 5% as stated in the current document. However, as stated previously, it would be more meaningful to separate weight loss from weight maintenance and to give consideration to weight prevention.

It is generally recognized that people with obesity experience a number of significant co-morbidities including diabetes and dyslipidema. We recommend that for agents where a sponsor foresees a significant benefit in a particular co-morbidity in addition to weight loss, and has plans to study this particular obese population for a dual indication, dual primary endpoints be considered. Given that a number of co-morbid variables may show improvement in addition to weight loss and that this information would greatly benefit the prescribers of these agents, it is important to have this information available in the product label. As such, it should not be necessary to declare a co-morbid endpoint as a co-primary endpoint in order for inclusion in the product label. For multiple co-morbid endpoints, each can be listed as secondary endpoints, but a multiplicity adjustment rule would need to be specified.

Furthermore, we strongly urge the FDA to consider the balance of benefit versus risk for an agent that modifies a disease state primarily through a mechanism of weight loss. An agent should be considered efficacious with the opportunity for a primary indication for that specific comorbid disease (e.g. type 2 diabetes, hypertension) if the effects are:

- Clinically relevant for that disorder
- In line with accepted clinical practice for that disorder
- The magnitude and the durability of effect is consistent or superior to other approved agents for that disorder

- An acceptable safety profile for that disorder
- The added benefit of weight loss, rather than being considered a barrier to an indication for these conditions, often adds to the accepted standard of care (e.g. type 2 diabetes, where this is an elusive clinical attribute with current interventions).

With reference to potential indications, we suggest the FDA consider the potential for a prevention of other metabolic diseases associated with obesity, (e.g. type 2 diabetes, dyslipidemia) where the sponsor demonstrates a significant reduction in the conversion of subjects with obesity to the metabolic disease (e.g. subjects with obesity and impaired glucose tolerance/impaired fasting glycemia to type 2 diabetics through drug plus diet/ exercise vs. diet/exercise alone).

In addition to the biomarkers currently listed in the guidance document it is suggested that the following additional CV biomarkers for assessment be considered where applicable for agents with potential to demonstrate benefit: left ventricular mass, inflammatory markers (e.g. C-reactive protein) and clotting factors (e.g. PAI-1 and fibrinogen).

It is suggested that in addition to the empirical assessment of body composition and body fat in all subjects through anthropometric measurements (e.g. waist circumference), these should also be adequately assessed in an appropriately powered subset of subjects via more accurate direct measurements (e.g. DEXA, CT, MRI, underwater weighing)

For drugs acting in the central nervous system, the potential for drug dependence or abuse should be discussed within the guidance.

5.3 DURATION OF TRIALS

Broadly we agree with the treatment durations and overall treatment exposures proposed in the guidance. However, if our previous suggestion is considered there should be guidance on the duration and exposure requirements for the weight loss and weight maintenance phase of obesity treatment, respectively. And this would be separate from the obesity or diabetes prevention requirements that should also be addressed.

It is suggested that maintenance of body weight be defined as relative to baseline and not relative to placebo, i.e. weight regain at the same trajectory, as placebo should not constitute maintenance. For a weight loss claim, a trial duration of 6 months would be adequate; for a weight maintenance claim, twelve months may be more than sufficient for the duration of the trial, since if the drug were not effective in maintaining the weight loss, this would become apparent early. For safety evaluation, a subset of patients may continue for a longer period (e.g. 24 months).

As per the current guidance *"For those who have dropped out of the study it is usually possible to obtain at least telephone contact at 24 months for self-reported weight, and morbidities."* This appears to envision combining data from the open label second year

with data from the randomized first year. Such combination of data may produce bias because the first year after study entry gets more protection from study entry criteria than does the second year. Additionally, such telephone follow-up requirements should be tailored for off-treatment monitoring of specific predefined safety concerns and not be used to assess post treatment weight or other efficacy parameters due to the potentially unreliable nature of data captured in this format. Consideration should also be given to historically poor compliance rates with such follow up strategies following study withdrawal.

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26 April 2004

Food and Drug Administration
Dockets Management Branch (HFA-305)
5630 Fishers Lane (Room 1061)
Rockville, MD 20852

RE: DOCKET NO. 2003D-0570: GUIDANCE FOR THE CLINICAL EVALUATION OF WEIGHT-CONTROL DRUGS [69 Federal Register 3588-3589 January 26, 2004]

Amylin Pharmaceuticals, Inc. is a biopharmaceutical company engaged in the discovery, development, and commercialization of drug candidates for the treatment of diabetes, obesity, and cardiovascular disease. The company's mission is to improve the lives of people with diabetes and other metabolic diseases through the discovery, development, and commercialization of innovative, cost-effective medicines. Because of its ongoing research in and commitment to obesity and obesity-related diseases, Amylin welcomes the opportunity to comment on the FDA draft guidance titled, "Guidance for the Clinical Evaluation of Weight-Control Drugs."

Amylin agrees that obesity is an urgent public health issue that requires more options for medical intervention. Recent scientific discoveries have greatly enhanced our understanding of the complex mechanism by which body weight is regulated. These discoveries have identified new potential therapeutic targets that hold promise of greater efficacy and safety than past weight loss medications. But there is a significant concern to any company that must decide whether to allocate millions of dollars to development of a drug for obesity due to the negative perception surrounding pharmacologic intervention. However, we are encouraged by the recent steps taken by the FDA to interact with industry to navigate the challenges, and better define the requirements, involved in the approval process for anti-obesity medications. Amylin recognizes that regulatory guidance on weight-loss drugs can only provide a framework, and not a "one size fits all" formula, for the development and approval process, and anticipates that the revised guidance will include language that encourages sponsors to discuss innovative approaches to arrive at conclusions that support safety and efficacy as a basis for drug approval. Specific comments to the guidance are attached. These comments are being provided electronically as directed in the Federal Register Notice.

Amylin Pharmaceuticals, Inc. appreciates the opportunity to submit these comments and looks forward to continuing dialogue with the Agency on this important issue. Should you have any questions concerning these comments, please contact me either by phone at (858) 642-7076 or by facsimile at (858) 334-1076.

Sincerely,

Christian Weyer, MD
Director
Clinical Research

CW/ch

2003D-0570 C9

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COMMENTS FROM
AMYLIN PHARMACEUTICALS, INC.
TO

GUIDANCE FOR INDUSTRY

GUIDANCE FOR THE CLINICAL EVALUATION OF WEIGHT-CONTROL DRUGS
(current draft guidance issued 1996)

26 April 2004

DOCKET NO. 2003D-0570
69 Federal Register 3588-3589, January 26, 2004

AMYLIN PHARMACEUTICALS, INC.
COMMENTS ON THE DRAFT GUIDANCE FOR THE CLINICAL EVALUATION OF WEIGHT-CONTROL DRUGS

Comment # 1

Guidance Reference: Page 2, Section 2
GENERAL RATIONALE

Current guidance reads, "*FDA standards for weight-control drug approval anticipate the investigation of long-term safety and efficacy of weight-control drugs, leading to approval of drugs with indications for weight control using long-term or indefinite drug administration.*"

Some anti-obesity drug candidates may be most effective for inducing weight loss, while others may be most effective in weight loss maintenance. A clear definition of regulatory requirements for a short-term weight loss, long-term weight loss, and weight maintenance indication would be desirable.

Comment # 2

Guidance Reference: Page 2, Section 3
EARLY CLINICAL TRIALS

Current guidance reads, "*The mechanism of action of the drug should be established if possible.*"

Many of the parameters required to establish the mechanism of action of an anti-obesity drug are rather difficult to measure in humans (e.g., food intake, hunger, energy expenditure, body composition). Weight loss mechanisms in animals may or may not be applicable to humans. More specific guidance might be useful as to the requirements for including findings on the mechanism of action into the package insert.

Comment # 3

Guidance Reference: Page 3, Section 4
DOSE RANGE FINDING

Current guidance reads, "*Dose-finding should identify the lowest dose of the drug that safely achieves an optimal drug effect. Inclusion of at least 3 doses of drug in dose-finding efficacy studies will probably allow identification of a low dose that is inadequate, and also a dose that achieves the maximum benefit that can be obtained without toxicity.*"

It is understood that dosage levels should be selected that allow identification of a low dose that is inadequate and a dose that achieves the maximum benefit that can be obtained without toxicity in order to establish a dose-response relationship. However, for some classes of products (those that cause little to no toxicity or those where tolerability differs widely among individuals), it may not be possible to define a general, "one-fits-all" maximum dose. In these cases, the guidance should define a procedure/strategy that allows a sponsor to provide a scientific justification of the rationale for the doses selected for Phase 3 clinical trials.

Comment # 4

Guidance Reference: Pages 3-6, Section 5
TRIALS TO ESTABLISH EFFICACY

Current guidance reads, *"Subjects who meet the entry criteria with regard to obesity and risk factors may be entered into a program aimed at weight reduction, but without drug. Such a program might include calorie-restricted or controlled diet, behavior modification, and exercise. As a minimum, a modestly restricted diet and regular exercise should be actively encouraged. Placebo may be used during this period so that placebo responders are identified. Generally, this program should be continued for 6 weeks. Subjects should not be placed on drug as long as weight loss continues without drug, but may be randomized when weight has plateaued, as long as their weight remains above their goal for weight reduction (e.g. ideal body weight). Although subjects who are still losing or who reach ideal body weight on this program have no need for drug at that time, they may be kept on the weight program and randomized to placebo or study drug later if their success at weight loss evaporates."*

In previous pivotal trials with anti-obesity agents (including sibutramine and orlistat), these guidelines were followed, and subjects, on average, lost weight prior to randomization. Thus, study medication was introduced at a stage when subjects had been in a negative energy balance for several weeks, and presumably had fully manifested the typical counterregulatory responses, e.g., activation of central orexigenic signals, decrease in metabolic rate. These compensatory responses may differentially interfere with the mechanism of action of different anti-obesity agents, possibly augmenting the effect of some agents, while diminishing the effect of others.

In clinical practice, most obese subjects have had many unsuccessful attempts to lose weight with diet and exercise alone, and by the time they seek drug treatment many will have recently (re-) gained weight (meaning that they will start study medication while in a positive, or neutral energy balance). In clinical practice, it is the exception, not the rule, that subjects will have lost several pounds of weight just prior to the time that drug treatment is initiated.

It therefore appears that the Phase 3 study design outlined in the 1996 guidance may not represent the scenario in which these drugs may later be used in the clinic. Thus, the requirement for a six-week run-in period where all subjects are encouraged to partake of a restricted diet and increase exercise intervention should be re-evaluated, as it is felt that this requirement may confound trial results and not reflect real world conditions.

Comment # 5

Guidance Reference: Pages 4-5, Section 5.2
Procedures

Current guidance reads, *"Measurement of obesity-associated cardiovascular risk factors (lipids, blood pressure and glucose tolerance) during drug administration is encouraged, as they may have a place in determining the balance of benefit vs. risk for the drug. If one or more of these factors deteriorates or is not improved, the risk associated with this deviation must be considered in making a benefit-to-risk decision for the drug."*

It is well established that most health risks associated with obesity increase exponentially with increasing BMI (i.e., subjects with a BMI of 40 are at a much greater risk than subjects with a BMI of 30). While the effect of pharmacologically induced weight loss on cardiovascular risk has not yet been established in hard endpoint trials, it is conceivable, if not likely that the benefit of drug-induced weight loss (in terms of absolute risk reduction and number-needed-to-treat) also increases with increasing BMI. In contrast, the risk (safety) of a given anti-obesity agent may be constant across a wide range of BMI categories. Consequently, an anti-obesity agent may have a favorable risk/benefit profile (approvable) in more severely obese subjects (e.g., BMI>35), but a less favorable risk/benefit profile (perhaps non-approvable) in moderately obese subjects (e.g., BMI 27-30). Based on the 1996 guidance, it is unclear whether and how a drug candidate might be approved for a high-risk BMI subcategory.

Comment # 6

Guidance Reference: Pages 4-5, Section 5.2
Procedures, Endpoint evaluation

Currently, at least two weight loss demonstrations of efficacy are possible:

a) demonstration that the drug effect is significantly greater than the placebo effect and the mean drug-associated weight loss exceeds the mean placebo weight loss by at least 5%.

b) demonstration that the proportion of subjects who reach and maintain a loss of at least 5% of their initial body weight is significantly greater in subjects on drug than in those on placebo.

Comment 1: Efficacy in relation to initial BMI – The guidance does not consider or address possible subpopulation indications.

For example, a drug candidate, based on its mechanism of action, may be much more effective in severely obese than in overweight or moderately obese subjects. Consider a scenario where a drug causes 4% weight loss in subjects with a BMI of 27-45 (not meeting current efficacy criteria), but 7% weight loss in subjects with a BMI >35, and only 2% weight loss in subjects with a BMI of 27-35. From this example, it is unclear whether the drug can be approved for severely overweight patients (BMI >35). A revised guidance document should including more specific guidance on the appropriate clinical trial strategy (separate trial or prospectively defined subgroup analysis) for possible subpopulation indications or treatments.

Comment 2: Efficacy in relation to risk factors/safety – The guidance does not address if a risk/benefit analysis may provide a reduction in the 5% threshold if the drug is safe or reduces other obesity related risk factors.

Consider two drug candidates:

Drug A causes 5-7% weight loss accompanied by little improvement in obesity-related risk factors (e.g., blood pressure, glucose tolerance) and some safety concerns (CNS side effects); whereas, Drug B causes 3-4% weight loss and is associated with marked improvements in obesity-related risk factors and has virtually no safety concerns.

In this scenario, Drug B may have greater therapeutic benefit in preventing obesity-related co-morbidities and is very safe, yet based on the current guidance, Drug A seems to have the better chance for approval because it achieves greater than a 5% weight loss.

The guidance should address whether the same "efficacy hurdle" be applied to all drug candidates regardless of their accompanying effect on risk factors and their safety profile.

Comment 3: Efficacy in conjunction with other, already approved drugs – Currently, the guidance only addresses monotherapy.

In type 2 diabetes, where a much larger armamentarium of drugs is available, and combination therapy is a standard treatment, Phase 3 trials are often designed in an add-on fashion. In obesity, where the number of currently marketed drugs is scarce, Phase 3 trials are typically designed as monotherapy trials. That is, every single drug candidate is required to cause at least a 5% weight loss on its own in order to reach the market. Obesity researchers tend to agree that it is unlikely that there will ever be a "magic bullet" that, in monotherapy, causes pronounced weight loss without side effects. Instead, the path for more pronounced, safe weight loss may lie in combination treatment with drugs that are moderately effective by themselves, but are more effective and safer when used in combination, possibly at lower doses (due to additive mechanism of actions and/or a synergy of effects).

A revised guideline should provide sufficient guidance on the regulatory/clinical trial strategy for the possible approval of an anti-obesity drug candidate for a combination therapy indication.

Comment # 7

Guidance Reference: Pages 5-6, Section 5.3
Duration of Trials

Current guidance reads, *"In order to obtain an adequate estimation of the safety of weight-control drugs for long-term administration, generally, about 1500 subjects are expected to complete 12 months with 200-500 of those subjects completing 24 months of study. Most often the double-blind status of the study is maintained for at least 1 year, at which time, placebo patients may be switched to drug and followed on open label for another 12 months to a total of 24 months for weight and development of obesity-related morbidities. For those who have dropped out of the study it is usually possible to obtain at least telephone contact at 24 months for self-reported weight, and morbidities."*

Currently, the draft guidance recommends that pivotal trials include a second year of open-label extension, primarily for the collection of data related to long-term safety. In some instances long-term safety data may be available for drugs that are already marketed for another indication or for which extensive long-term safety data are available from previous development programs designed for related indications. Should this be the case and the dose for both development plans are comparable, use of this long-term data may be considered relevant.

2003D-0570 - Guidance for Industry: GUIDANCE FOR THE CLINICAL EVALUATION OF WEIGHT- CONTROL DRUGS; Availability

FDA Comment Number : EC4

Submitter : Dr. Christian Weyer **Date & Time:** 05/03/2004 05:05:36

Organization : Amylin Pharmaceuticals, Inc.

Drug Industry

Category :

Issue Areas/Comments

GENERAL

GENERAL

Amylin Pharmaceuticals, Inc. is a biopharmaceutical company engaged in the discovery, development, and commercialization of drug candidates for the treatment of diabetes, obesity, and cardiovascular disease. The companys mission is to improve the lives of people with diabetes and other metabolic diseases through the discovery, development, and commercialization of innovative, cost-effective medicines. Because of its ongoing research in and commitment to obesity and obesity-related diseases, Amylin welcomes the opportunity to comment on the FDA draft guidance titled, Guidance for the Clinical Evaluation of Weight-Control Drugs.